(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 516 410 B1

# (12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
**29.07.1998 Bulletin 1998/31**

(51) Int Cl.[6]: **C07C 401/00**, C07F 7/18, C07F 9/53

(21) Application number: **92304837.5**

(22) Date of filing: **28.05.1992**

## (54) Novel synthesis of 19-nor vitamin D compounds

Neues Herstellungsverfahren zur 19-nor Vitamin-D-Verbindungen

Nouveau procédé pour la préparation des composés 19-nor vitamine D

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE**

(30) Priority: **28.05.1991 US 705917**

(43) Date of publication of application:
**02.12.1992 Bulletin 1992/49**

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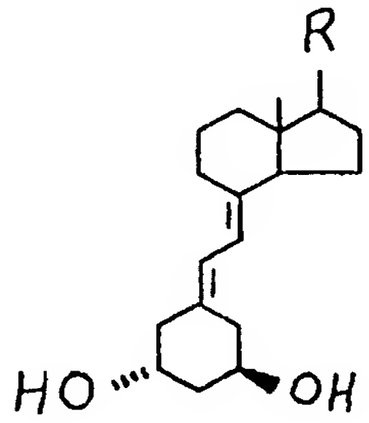
## Description

The hormone, 1α,25-dihydroxyvitamin D3, is known to be a highly potent regulator of calcium homeostasis in animals, and more recently its activity in cellular differentiation has been established, V. Ostrem, Y. Tanaka, J. Prahl, H. F. DeLuca and N. Ikekawa, Proc. Natl. Acad. Sci. USA, (1987), 84, 2610. Many structural analogs have been prepared and tested and some of these have been found to exhibit an interesting separation of activities in cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of some cancers and osteoporosis, H. Sai, S. Takatsuto, N. Ikekawa, I. Tanaka and H. F. DeLuca, Chem. Pharm. Bull., (1986), 34, 4508.

Recently, a new class of vitamin D analogs has been discovered, the so-called 19-nor-vitamin D compounds, which, as shown by the general structure below, are characterized by the replacement of the ring A-exocyclic methylene group (carbon 19), typical of the vitamin D system, by two hydrogen atoms, for example 19-nor-1α-hydroxyvitamin $D_3$ and 19-nor-1α,25-dihydroxyvitamin $D_3$.

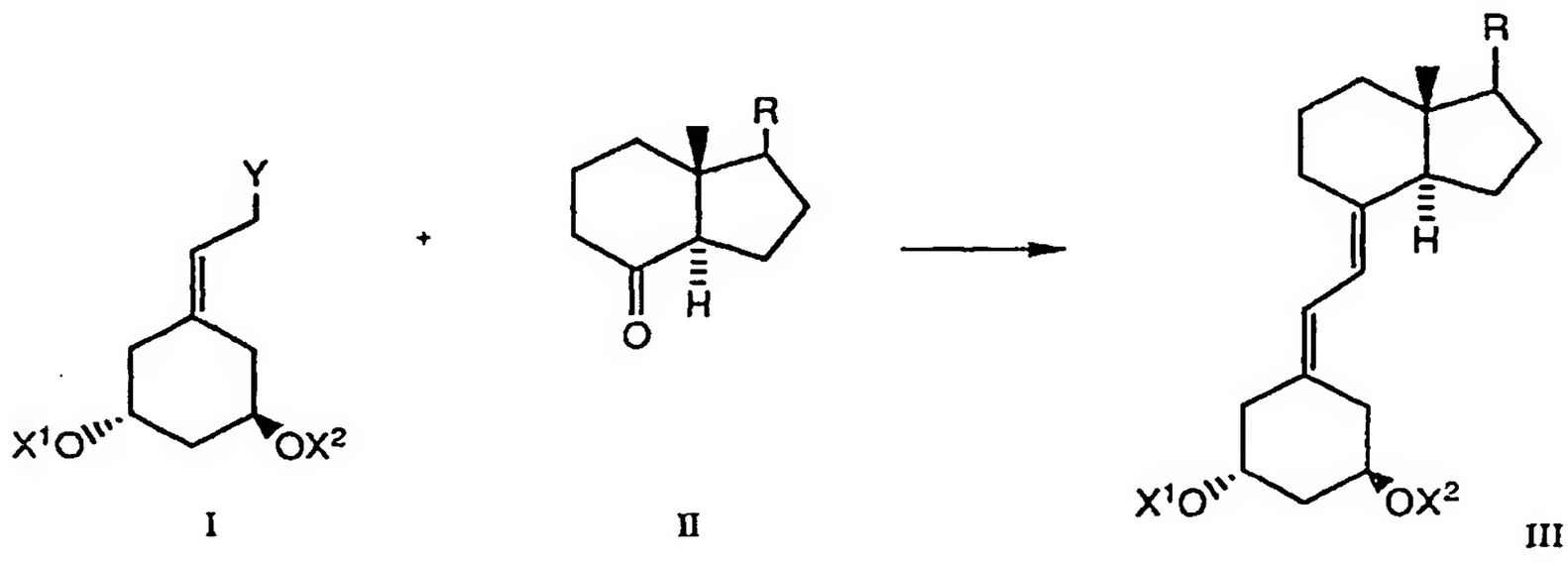



The group R in the above structure represents a steroid side chain as it occurs in any of the natural vitamin D compounds, or in synthetic analogs thereof. A specific example of a 19-nor-vitamin D compound is given by structure **20** in Scheme IV herein. Biological testing of such 19-nor-analogs (e.g. compound **20**) revealed an activity profile characterized by high potency in inducing differentiation of malignant cells, with very low calcium mobilizing activity. Thus, such compounds are potentially useful as therapeutic agents for the treatment of malignancies.

A method of synthesis of 19-nor-vitamin D compounds has been reported by Perlman et al., Tetrahedron Letters 13, 1823 (1990) and also EP-A-0 387 077. However, this method, which involves the removal of the C-19-methylene group in an existing vitamin D compound is not well suited for the larger scale preparation of 19-nor analogs.

## Disclosure of the Invention

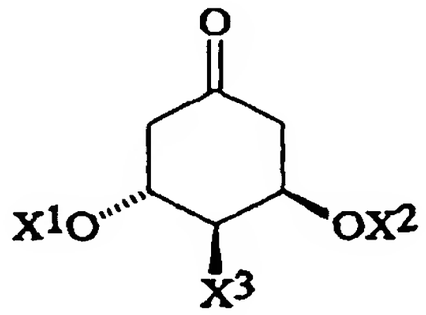
Described herein is a novel synthesis of 19-nor-vitamin D compounds. A characteristic element of this new method is the condensation of a ring-A unit, as represented by structure I, below, with a bicyclic-ketone of the Windaus-Grundmann type, structure II below, to obtain the desired 19-nor-vitamin D compound, structure III.



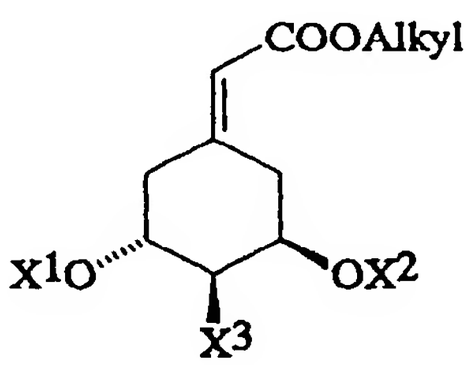

I II III

The process shown above, therefore, represents a novel application of the convergent synthesis concept, which has been applied effectively for the preparation of vitamin D compounds [e.g. Lythgoe et al., J. Chem. Soc. Perkin Trans. I, 590 (1978); 2386 (1976); Lythgoe, Chem. Soc. Rev. 9, 449 (1983); H. T. Toh and W.H. Okamura, J. Org. Chem. 48, 1414 (1983); E.G. Baggiolini et al., J. Org. Chem. 51, 3098 (1986); Sardina et al., J. Org. Chem. 51, 1264 (1986); J. Org. Chem. 51, 1269 (1986) as well as EP-A-0154185 and WO90/09992].

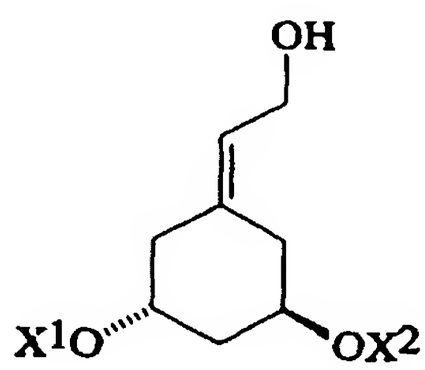
According to the present invention, there is provided a method of making a 19-nor vitamin D compound which comprises the steps of condensing a ketone of the structure:



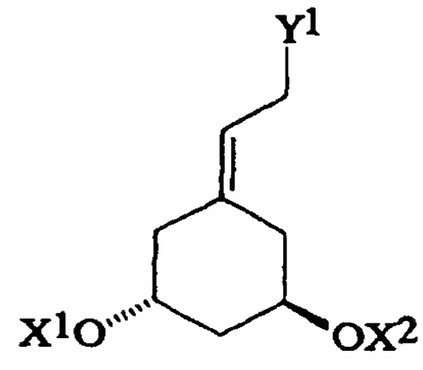

where $X^1$ and $X^2$ are each a hydroxy-protecting group, and $X^3$ is hydrogen or hydroxy, in the presence of a strong base to obtain an ester having the structure:



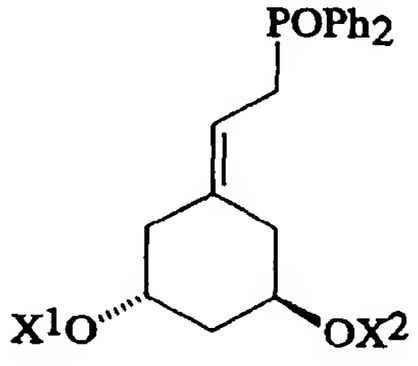

where $X^1$, $X^2$ and $X^3$ are as defined above, and "Alkyl" represents a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, with the proviso that when $X^3$ in the above ketone is a hydroxy function, that hydroxy function be first protected with a hydroxy-protecting group prior to the base-promoted condensation reaction, reducing said ester to obtain the allylic alcohol having the structure:




where $X^1$ and $X^2$ are as defined above, with the proviso that if $X^3$ in the above ester is a protected hydroxy function that function is removed by removing the protecting group and converting the resulting free alcohol to a thiono ester derivative which is subjected to a reductive free radical deoxygenation reaction, converting said allylic alcohol to a derivative having the structure:

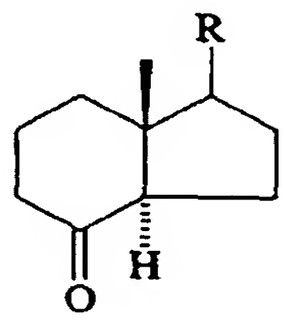


where $Y^1$ is halogen, which is I, Br or Cl, or an O-tosyl or O-mesyl group, and where $X^1$ and $X^2$, which may be the same or different, are hydroxy-protecting groups, converting said derivative to the phosphine oxide:

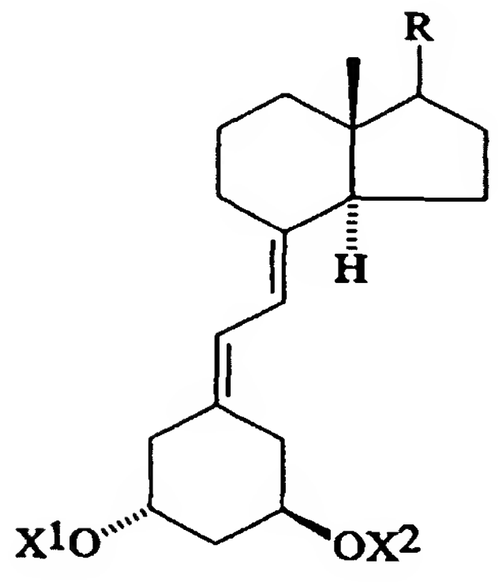


where $X^1$ and $X^2$ are as defined above by treatment of said derivative with a metal diphenylphosphide and a subsequent peroxide oxidation:

reacting the phosphine oxide with a ketone of the structure:



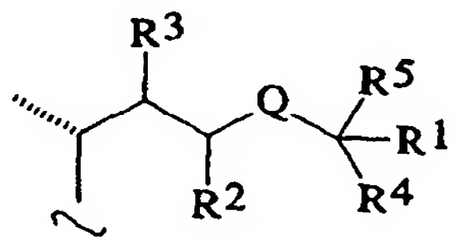
where R is hydrogen or the side chain of a vitamin D compound as defined below to produce a 19-nor-vitamin D compound of the structure:



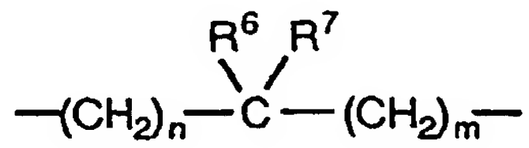
where $X^1$, $X^2$ and R are as defined above, and subsequently, if desired, removing one or more hydroxy-protecting groups.

An important aspect of this invention is the preparation of ring-A units of general structure I from (-)quinic acid. In structure I, above, $X^1$ and $X^2$, which may be the same or different, represent hydroxy-protecting groups, and Y represents a grouping that renders the hydrogen on the adjacent carbon center sufficiently acidic to yield a reactive carbanion upon treatment with a strong base. Exemplary of such groupings Y are $-P(O)Ph_2$, $-P(O)(OAlkyl)_2$, $-SO_2Ar$, or $-Si(Alkyl)_3$. Compounds of type I, above, are new. Their synthesis, and other novel intermediates used in their preparation are disclosed herein.

In the bicyclic-ketone of structure II, or in the 19-nor-vitamin D compound of structure III, above, the substituent R may represent hydrogen or a side chain of a vitamin D compound, it being understood that any functionalities in R that might be sensitive, or that interfere with the condensation reaction, be suitably protected as is well-known in the art. Thus, R represents hydrogen, alkyl, hydroxyalkyl, deuteralkyl, fluoroalkyl, or a side chain of the formula



where $R^1$, $R^2$, $R^3$, independently represent hydrogen, hydroxy, protected hydroxy, or alkyl, where the bond between carbons 22 and 23 may be a single, double or triple bond, where Q is the group



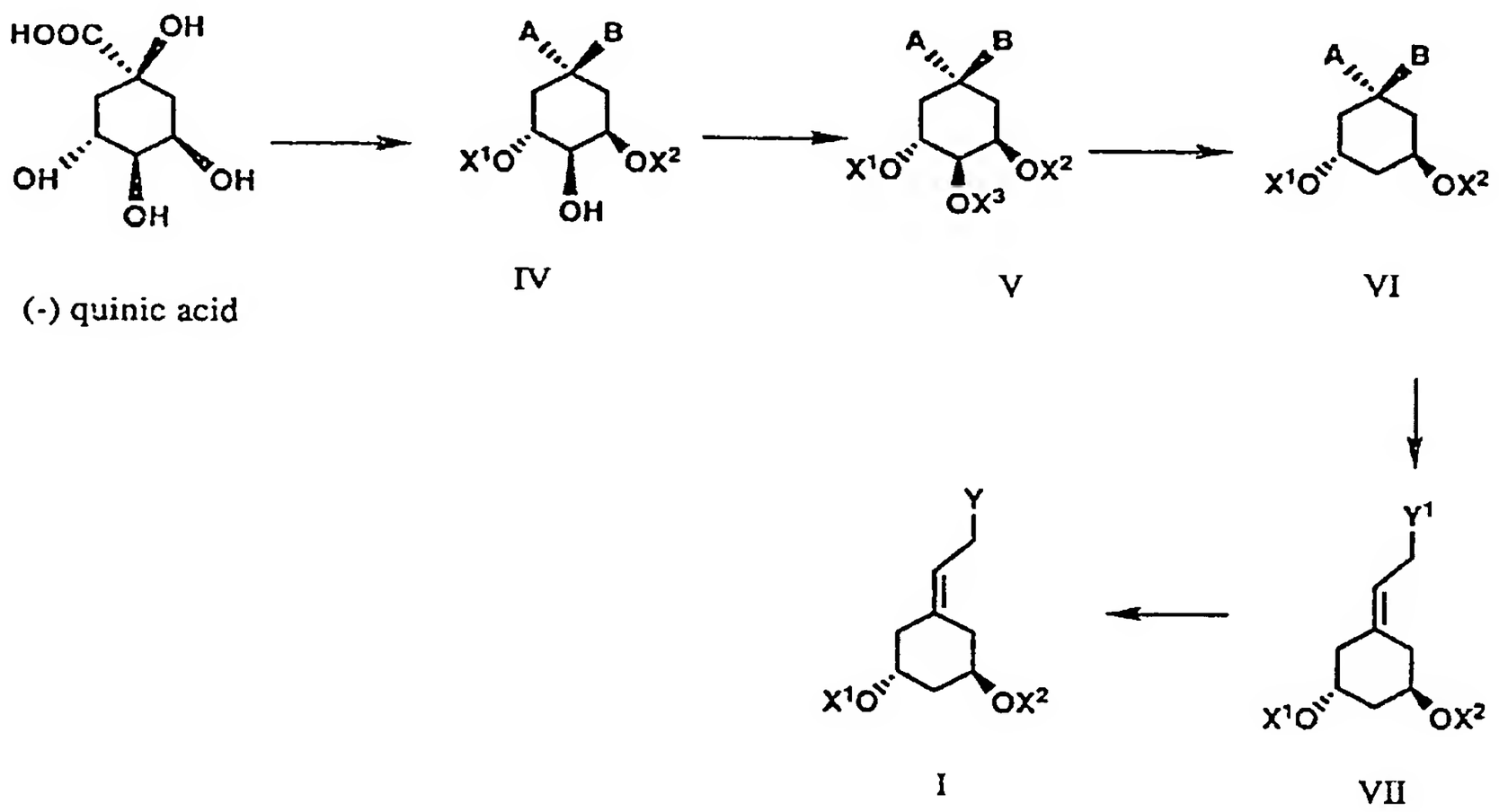
where $R^6$ and $R^7$, independently, are selected from hydrogen, alkyl, hydroxyalkyl, hydroxy, protected hydroxy, and fluoro, or where $R^6$ and $R^7$ taken together represent an oxo group or an alkylidene group, and where n and m are integers having, independently, the values 0, 1, 2, 3, 4 or 5,
where $R^4$ and $R^5$, independently, represent deuteroalkyl, fluoroalkyl and the group Q-H, or $R^4$ and $R^5$, taken together, represent the group Q, with the proviso that at least one of n or m has the value of 1 or greater, and wherein the carbon at any one of positions 20, 22 or 23 in the side chain may be replaced by an O, S, or N atom.

As used herein, the term "hydroxy-protecting group" refers to any group commonly used for the protection of hydroxy functions during subsequent reactions, including, for example, acyl or alkylsilyl groups such as trimethylsilyl,

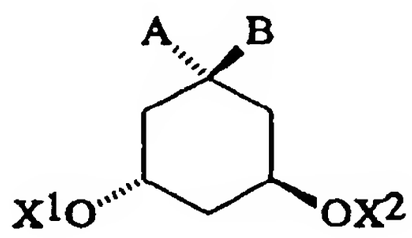
triethylsilyl, t-butyldimethylsilyl and analogous alkyl or arylsilyl radicals, or alkoxyalkyl groups such as methoxymethyl, ethoxymethyl, methoxyethoxymethyl, tetrahydrofuranyl or tetrahydropyranyl. A "protected-hydroxy" is a hydroxy function derivatized by one of the above hydroxy-protecting groupings "Alkyl" represents a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in all its isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, etc., and the terms "hydroxyalkyl," "fluoroalkyl" and "deuteroalkyl" refer to such an alkyl radical substituted by one or more hydroxy, fluoro or deuterium groups respectively. An "acyl" group is an alkanoyl group of 1 to 6 carbons in all its isomeric forms, or an aroyl group, such as benzoyl, or halo-, nitro- or alkyl-substituted benzoyl groups, or an alkoxycarbonyl group of the type Alkyl-O-CO-, such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, etc., or a dicarboxylic acyl group such as oxalyl, malonyl, succinoyl, glutaroyl, or adiopoyl. The term "aryl" signifies a phenyl-, or an alkyl-, nitro- or halo-substituted phenyl group. The term alkoxy signifies the group alkyl-O-. Keton es of general structure II featuring homologated side chains are new compounds.

Ketones of structure II, with diverse side chain groups R, can be prepared by known methods, as documented, for example by Baggiolini et al., J. Org. Chem. 51, 3098 (1951); Baggiolini et al., U.S. Patent 4,804,502; Sardina et al., J. Org. Chem. 51, 1264 (1986); Kocienski et al., J. Chem. Soc. Perkin Trans. 1, 834 (1978); Toh and Okamura, J. Org. Chem. 48, 1414 (1983); Mascovenas et al., J. Org. Chem., 51, 1269 (1986). Ketones of general structure II featuring homologated side chains are new compounds.

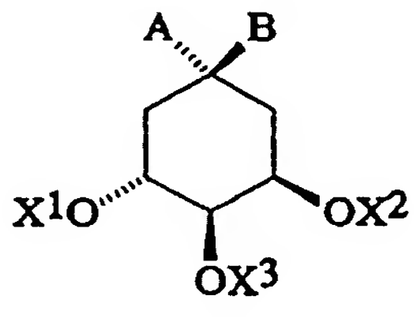
For the preparation of ring A-synthons of structure I, a new synthetic route has been developed, based on (-)quinic acid as starting material. This substance, being commercially available and having hydroxy groups of the correct stereochemistry in desired positions is a useful synthon in vitamin D chemistry [Desmaele and Tanier, Tetrahedron Letters, 26, 4941 (1985)]. The overall process, in general form, is summarized by the reaction scheme below:



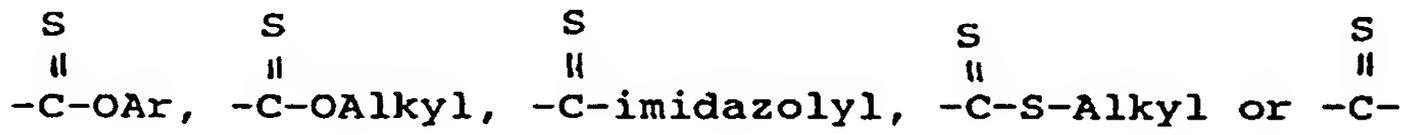

Accordingly, the present invention also provides a process for making a compound of the formula:



wherein $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group, A is -COOAlkyl or $-CH_2OH$ and B is hydroxy, or A and B together represent either oxo or = CHCOOAlkyl, where "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, which comprises eliminating the group in the 4-position in a compound of the formula:

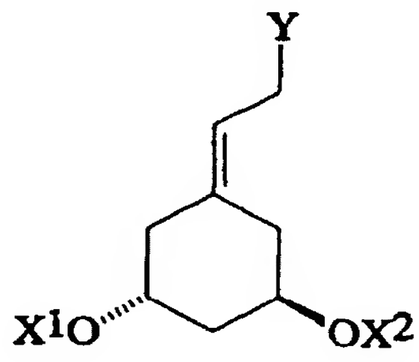



where $X^3$ is

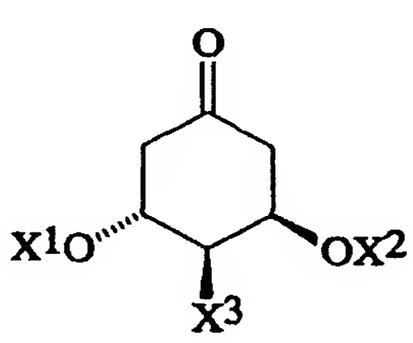



S-Ar, said Ar

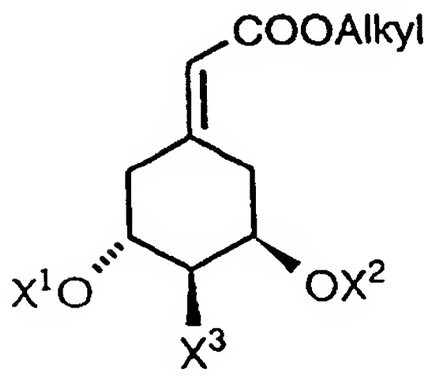
representing a phenyl, or an alkyl-, nitro-, or halo-substituted phenyl, and said alkyl is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form by subjecting said compound to a reductive free radical deoxygenation reaction and also a method of making a compound of the formula X:



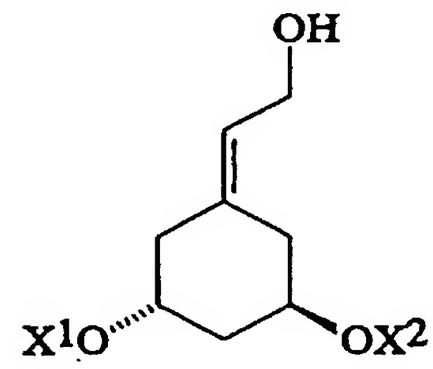

wherein each of $X^1$ and $X^2$, which may be the same or different is hydrogen or a hydroxy-protecting group and Y is hydroxy, halogen, O-mesyl, O-tosyl or a hydroxy-protecting group, which comprises condensing a ketone of the structure:



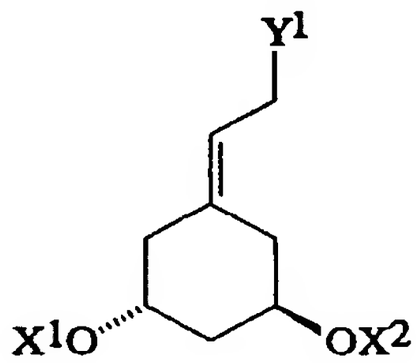

where each of $X^1$ and $X^2$, which may be the same or different, is a hydroxy-protecting group, and $X^3$ is hydrogen or hydroxy, in the presence of a strong base to produce an ester of the formula:



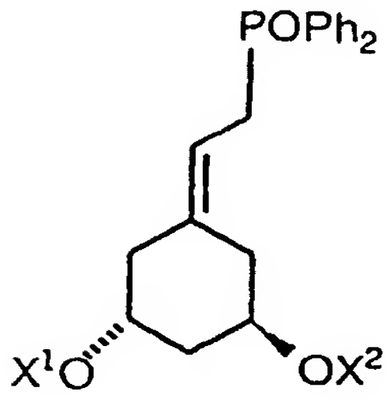

where $X^1$, $X^2$ and $X^3$ are as defined above, and "Alkyl" represents a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, with the proviso that when $X^3$ in the above ketone is a hydroxy function, that hydroxy function be first protected with a hydroxy-protecting group prior to the base-promoted condensation reaction, reducing said ester to produce an alcohol of the formula:



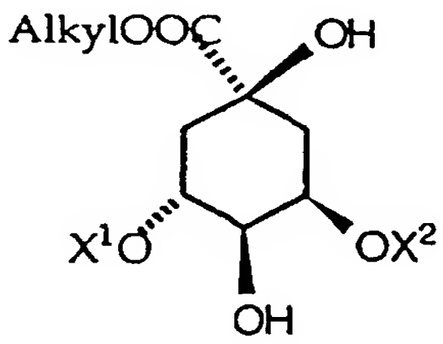

where $X^1$ and $X^2$ are as defined above, and optionally converting said alcohol to its corresponding halogen, which is I, Br or Cl, O-tosyl, O-mesyl or hydroxy-protecting derivative and optionally removing the hydroxy-protecting groups $X^1$ and $X^2$, with the proviso that if $X^3$ in the above ester is a protected hydroxy function, that function is eliminated prior to the reduction reaction by removing the protecting group and subjecting the thiono-ester derivative of the alcohol to a reductive free radical deoxygenation reaction and, optionally, converting compound of formula X to certain compounds of the formula:



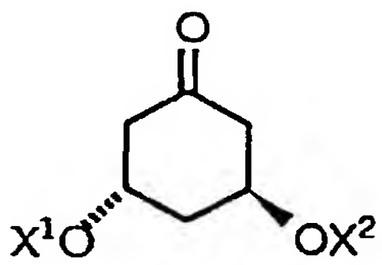

wherein each of $X^1$ and $X^2$, which may be the same or different is hydrogen or a hydroxy-protecting group and $Y^1$ is $-POPh_2$, $-Si(Alkyl)_3$, $-PO(OAlkyl)_2$, or $-SO_2Ar$, said Ar representing a phenyl or an alkyl-, nitro-, or halo-substituted phenyl, and said alkyl is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form as discussed below for the conversion of the alcohol. The present invention also provides a method of making the phosphine oxide of the formula:



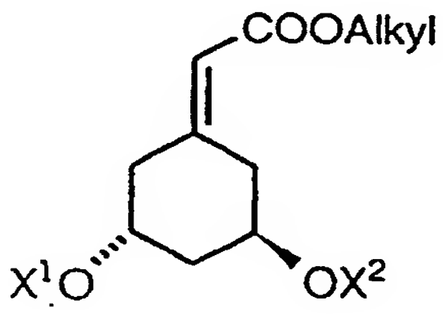

wherein each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group which comprises eliminating the 4-hydroxyl group of a quinic acid of the formula:



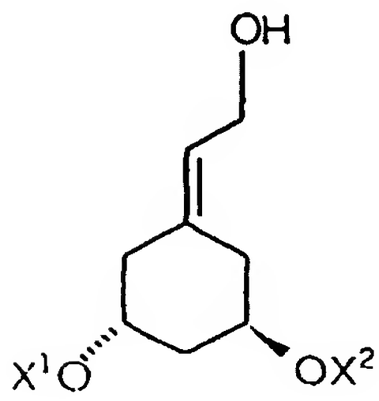

where each of $X^1$ and $X^2$, which may be the same or different, is a hydroxy-protecting group and "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form by treating the corresponding thiono-ester with a hydrogen radical source in the presence of a radical initiator, converting the resulting dehydroxylated compound to a ketone of the formula:




wherein $X^1$ and $X^2$ are as defined above, by treating the deoxygenated compound with a hydride reducing agent followed by oxidative cleavage of the resulting vicinal diol, condensing the ketone in the presence of alkyl (trimethylsilyl) acetate and a strong base to produce an ester of the formula:




wherein $X^1$ and $X^2$ and "alkyl" are as defined above, reducing said ester to produce an alcohol of the formula:

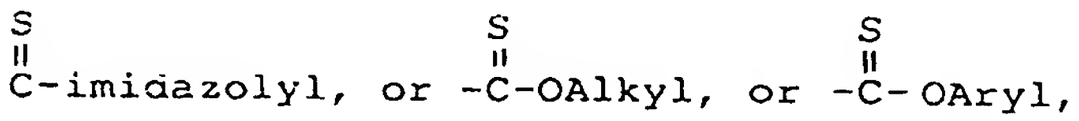


As shown in this scheme, the conversion of quinic acid to the desired ring-A unit I comprises two major synthetic transformations, namely the removal of the central hydroxy group at carbon-4 of quinic acid, and the replacement of the carboxy and hydroxy substituents of carbon-1 by an unsaturated two-carbon side chain bearing the desired Y-functionality. It was found that the overall process can be executed in several, conceptually related variations, differing chiefly in the order in which the key synthetic operations are accomplished.

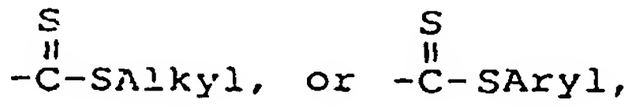
In the above structures (IV, V, VI), $X^1$ and $X^2$, which may be the same or different, represent a hydroxy-protecting group, A represents the group -COOAlkyl or $-CH_2OH$, B is hydroxy, and A and B, when taken together, represent an oxo group (=O), or =CHCOOAlkyl.

The initial steps of the overall process comprise the esterification of quinic acid, by treatment with a suitable alkyl alcohol (e.g. methanol, ethanol, propanol or higher alkanol) under acid catalysis, followed by hydroxy protection under conditions known in the art, to provide compound IV, where A is -COOAlkyl, B is hydroxy, and $X^1$ and $X^2$ are hydroxy-protecting groups. While the specific nature of $X^1$ and $X^2$ is not critical, it is understood, of course, that the protecting groups selected are both compatible with subsequent chemical transformation, and also removable when desired. Suitable are, for example, alkylsilyl- or alkylarylsilyl groups or alkoxyalkyl groups. By appropriate further transformation of the above hydroxy-protected alkyl ester, e.g. by hydride reduction of ester (thereby producing compound IV, where A is $-CH_2OH$, and B is -OH), followed by cleavage of the resulting vicinal diol, using known vicinal diol cleavage reagents, such as periodate or lead tetracetate, there is obtained the corresponding cyclohexanone derivative, i.e. compound IV, where A and B, taken together represent an oxo function and $X^1$ and $X^2$ are hydroxy-protecting groups. This ketone, in turn, after temporary protection of the remaining central hydroxy group at C-4 (e.g. acyl, alkylsilyl or alkoxyalkyl protection) can be alkylated, for example, by treatment with alkyl (trimethylsilyl) acetate in the presence of a strong base, such as NaH, lithium diisopropylamide, or an alkyl or aryl lithium base, to obtain, after removal of the temporary C-4-OH-protecting group, the alkyl cyclohexylidene ester, of general structure IV, where A and B, taken together represent the group =CHCOOAlkyl, and $X^1$ and $X^2$ are hydroxy-protecting groups.

It has been found that intermediate IV in all of the above described structural modifications can be used for the reductive removal of the C-4-hydroxy group, by means of a free radical deoxygenation procedure [Barton and McCambie, J. Chem. Soc. Perkin Trans. 1, 1574 (1975); Robins et al., J. Am. Chem. Soc. 103, 933 (1981); 105, 4059 (1983); Barton and Motherwell, Pure & Appl. Chem., 53, 15 (1981)]. This process entails the conversion of the free C-4-hydroxy group in compound IV to a suitable derivative, for example, a thiono-ester or xanthate derivative, as represented by general structure V in the above reaction scheme, where $X^3$ is
a grouping such as



or



and where A, B, $X^1$ and $X^2$ have the meaning previously defined. Intermediates of type V, upon treatment with a

hydrogen radical source in the presence of a radical initiator, then undergo reductive deoxygenation to furnish compounds of general structure VI, where A, B, $X^1$ and $X^2$ represent substituents as previously defined. For such deoxygenation reactions, suitable sources of hydrogen radicals are the trialkyltin hydrides (e.g. tributyltin hydride) or tris (trialkylsilyl)silanes (e.g. $(Me_3Si)_3SiH$) [Schummer and Hofle, Syn. Lett. 106 (1990); Ballestri et al., J. Org. Chem. 56, 678 (1991)], and suitable radical initiators are provided by azaisobutyronitrile (AIBN) or by irradiation. It is to be noted that the substituents A, B,
$X^1$ and $X^2$ remain unchanged during the above described two-step deoxygenation procedure. Thus, from compound IV, where A is -COOAlkyl and B is -OH, there is obtained compound VI, where A is -COOAlkyl, and B is -OH, and likewise, compound IV, where A and B, taken together represent =O, or =CHCOOAlkyl, yields compound VI, where A and B together, represent =O, or =CHCOOAlkyl, respectively.

As in the case of the compounds of structure IV, it is possible to effect transformations of the A and B substituents of the compounds of structure VI by processes entirely analogous to those discussed in connection with the compounds of structure IV. Thus, compound VI, where A is COOAlkyl and B is hydroxy, upon ester reduction and vicinal diol cleavage, as described above for the case of compound IV, provides VI as the cyclohexanone analog, where A and B, taken together represent an oxo group, and the latter, upon alkylation as described above, yields the cyclohexylidene modification, i.e. VI, where A and B taken together represent =CHCOOAlkyl.

For the subsequent steps towards the preparation of ring A-synthon of general structure I, the cyclohexylidene ester VI, where A and B together represent =CHCOOAlkyl, and $X^1$ and
$X^2$ signify hydroxy-protecting groups, is the desired intermediate. These subsequent steps comprise, first, the reduction of the ester (using, for example, $LiAlH_4$ or diisobutylaluminum hydride, DIBAL-H) to the corresponding primary alcohol of structure VII, shown below, where $X^1$ and $X^2$ represent hydroxy-protecting groups, and $Y^1$ is hydroxy. This alcohol, under conventional tosylation or mesylation conditions, may be transformed to the corresponding tosylate or mesylate, structure VII, where $Y^1$ represents $-O-SO_2PhMe$, or $-OSO_2Me$, or, alternatively, the alcohol may be subjected to displacement by halogen, to obtain the corresponding halide, structure VII, where $Y^1$ is a halogen atom, i.e. I, Br or Cl. From the mesylate, tosylate or halide of structure VII, the desired synthon of structure I is now obtained by various generally known conversion reactions. Thus, the halide, tosylate or mesylate, upon treatment with a metal diphenylphosphide and subsequent peroxide oxidation, yields the desired phosphine oxide derivative of structure I, where $Y=-P(O)Ph_2$. Similarly, the halide upon treatment with triethylphosphite under Arbuzov reaction conditions, provides the corresponding phosphonate derivative I, where $Y=-P(O)(OEt)_2$. From the tosylate or mesylate, upon displacement with the sodium salt of an arylsulfinic acid, there can be obtained the aryl-sulfone derivative of compound I, where $Y=-SO_2Ar$. Likewise, upon reaction of the halide VII with trichlorosilane followed by alkylation with an alkylhalide, there is obtained the alkylsilane derivative of compound I, where $Y=-Si(Alkyl)_3$.

The condensation reaction is advantageously conducted by treating the ring A unit of general structure I, dissolved in an organic solvent, with a strong base (e.g. an alkali-metal hydride, alkyl- or aryl lithium, or a lithium alkylamide reagent), so as to generate the anion of I, and then allowing this anion to react with ketone II, so as to achieve condensation to the 19-nor-vitamin analog III, either directly, or via intermediates (e.g. in the case of condensations with compound I where $Y=SO_2Ar$) transformable to III according to known procedures. Any hydroxy-protecting groups (i.e. protecting groups $X^1$ and $X^2$ and/or hydroxy-protecting groups that may be present in the side chain) can then be removed by appropriate hydrolytic or reductive procedures known in the art, such as hydride reduction, to obtain the free hydroxy-vitamin analog, structure III, where $X^1$ and $X^2$ represent hydrogen.

## Typical Embodiments of the Invention and Specific Examples

More specific embodiments of the preparation of the above described ring-A unit are outlined in Schemes I, II, and III, whereas Scheme IV provides a specific embodiment of the condensation reaction to obtain a desired 19-nor-vitamin D compound. In the following description and subsequent examples, Arabic numerals (e.g. **1**, **2**, **3**, etc.), designating specific synthetic products, refer to the structures so numbered in the Schemes.

As shown in Scheme I, the starting material for the preparation of the ring-A unit is the commercially available (1R, 3R,4R,5R) (-) quinic acid, designated as compound **1** in Scheme I herein, which already contains the correct stereochemistry of the 1- and 3-hydroxy groups for the desired 19-nor-vitamin D compound. Esterification with methanol in the presence of a catalytic amount of acid (e.g. p-toluene sulfonic acid), followed by treatment with tert-butyldimethylsilyl chloride and triethylamine in dimethyl formamide gave the protected methyl ester **2**. It should be noted that esterification with higher alkanols (e.g. ethanol, propanol, etc.) under analogous conditions produces the corresponding higher esters, and that similarly other hydroxy-protecting groups (e.g. other alkyl or arylsilyl groups, or alkoxyalkyl groups) can be introduced at this stage by known methods. Such alternative esters or hydroxy-protected derivatives of **2** can likewise be used in subsequent conversions according to Schemes I, II or III. Reduction of the ester with diisobutylaluminum hydride gave triol **3**, and subsequent sodium periodate oxidation produced the cyclohexanone derivative **4**. The 4-hydroxy group was protected with an alkylsilyl group to give **5**. It is to be noted that because of the symmetry of these

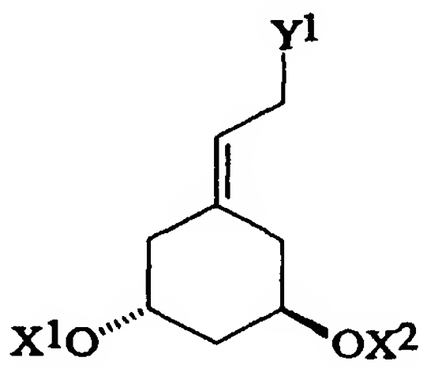
ketone intermediates (compounds **4** and **5**), the C-4-oxygen substituent can now be depicted as having either the α- or the β-stereochemical orientation. Hence, in accord with convention, the bond to the C-4-oxygen substituent in compounds **4** and **5** is indicated by a wavy line (∼∼). Three of the subsequent intermediates (compounds **6**, **7**, and **8**) are then obtained as pairs of products, one having the C-4-oxygen substituent in the α-, the other in the β-orientation. This fact is also denoted by a wavy-line bond to the C-4-oxygen substituent in structure **6**, **7**, and **8** of Scheme I.

A Peterson reaction with ethyl (trimethylsilyl)acetate in the presence of base in anhydrous tetrahydrofuran gave the unsaturated ester **6**. Other alkyl (trimethylsilyl)acetate esters (e.g. where alkyl=methyl, propyl, butyl, etc.) can be used in this reaction to give alkyl esters analogous to **6** (e.g. the corresponding methyl, propyl, butyl esters, etc.). Partial deprotection of the 4-trimethylsilyloxy group with dilute acetic acid in tetrahydrofuran gave **7**. The deoxygenation of the 4-hydroxy group was accomplished by a free radical fragmentation procedure [D. H. R. Barton and S. W. McCombie, J. Chem. Soc. Perkin Trans. 1, 1574 (1975); D. H. R. Barton and W. B. Motherwell, Pure & Appl. Chem., 53, 15 (1981)]. Thus, ester **7** was converted to the corresponding thioimidazolide **8** by treatment with 1,1-thioicarbonyldiimidazole in an organic solvent, and subsequent radical deoxygenation with tributyltin hydride in the presence of a radical initiator (AIBN) gave the protected cyclohexylidene ester **9**. The latter was reduced to the allylic alcohol **10** with diisobutylaluminum hydride which was then converted to the allylic chloride **11** by reaction with the complex made from N-chlorosuccinimide and dimethyl sulfide (E. J. Corey, C. U. Kim, M. Takeda, Tetrahedron Letters, 4339 (1972)] and finally transformed to the desired phosphine oxide **12** on treatment with lithium diphenylphosphide followed by oxidation with hydrogen peroxide.

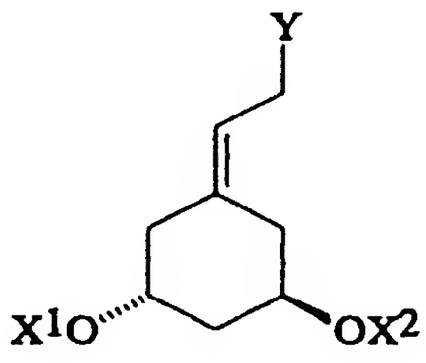
Scheme II illustrates an alternative method of synthesizing the ring-A unit. In this method, ester **2**, obtained as in Scheme I, is directly subjected to the free radical deoxygenation procedure, involving conversion to the thioimidazolide **13**, and subsequent treatment with tributyltin hydride to obtain the ester **14**. Reduction of compound **14** with diisobutylaluminum hydride (DIBALH) gave diol **15** followed by sodium periodate oxidation to the cyclohexanone derivative **16**. Subsequent olefination with ethyl (trimethylsilyl) acetate in the presence of base gave the protected cyclohexylidene ester **9**, which is then further processed to the phosphine oxide **12** in the same manner as described in connection with Scheme I.

Scheme III shows yet another modification of the preparation of the ring A-unit. Here the intermediate **4**, described previously (see Scheme I), is subjected to free radical deoxygenation procedure using conditions analogous to those described in connection with Scheme I and II. Thus, compound **4** is converted to the thionoimidazol **17** and then reacted with tributyltin hydride in the presence of AIBN to obtain the cyclohexanone derivative **16**. Further processing of this material, as in Scheme I and Scheme II, then provides phosphine oxide 12.

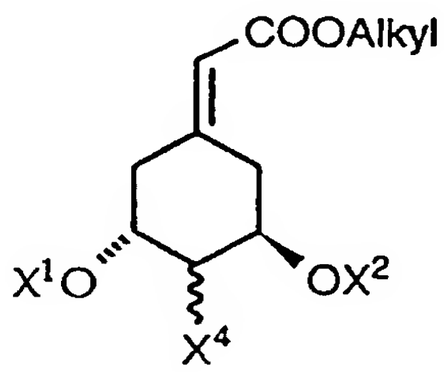
In addition to the desired ring-A synthons of general structure I, above, in particular those of structure:



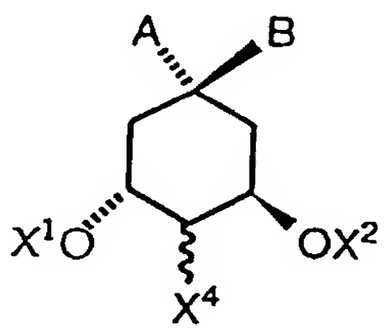

where each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group and $Y^1$ is hydroxy, protected-hydroxy, O-tosyl, O-mesyl, bromine, chlorine or iodine, and those of structure:



where each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group, and where Y is $-POPh_2$, or $-PO(OAlkyl)_2$, or $-SO_2Ar$, or $-Si(Alkyl)_3$, said Ar representing a phenyl, or an alkyl-, nitro- or halo-substituted phenyl, and said alkyl is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, the processes provide other novel intermediates. New compounds are, for example, the intermediates of general structure VII, above, or the cyclohexylidene esters of general structures IV, V and VI, above, where A and B, taken together, represent =CHCOOAlkyl, and of which specific embodiments are illustrated by structures 6, 7, 8, and 9 in Scheme I, in particular those of structure:




where each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group, $X^4$ is hydrogen, hydroxy, or protected hydroxy, and "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form and those of structure:




where each of $X^1$ and $X^2$, which may be the same of different, is hydrogen or a hydroxy-protecting group, $X^4$ is hydrogen, and A is -COOAlkyl or $-CH_2OH$, where "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbon atoms in any isomeric form, and B is hydroxy or A and B together represent an oxo group. Likewise, new are 4-deoxy intermediates of structure VI, above, where A is COOAlkyl, $-CH_2OH$, B is OH, or where A and B, together, represent an oxo group, which examples are provided by structures **14**, **15**, and **16** in Scheme II. It is also important to note that although these intermediates are generally used in their hydroxy-protected form in the various processes discussed above, the hydroxy-protecting groups ($X^1$, $X^2$, $X^3$) may also be removed, under conditions known in the art, to obtain the corresponding free-hydroxy-intermediates (compounds I, IV, V, VI and VII, where $X^1$ and/or $X^2$ and/or $X^3$ represent H) or be replaced by alternative hydroxy-protecting groups.

In Scheme IV is outlined a specific embodiment of the condensation reaction between phosphine oxide **12** (Scheme I) and a suitable ketone (structure **18**) representing rings C and D plus sidechain of the desired 19-nor-vitamin compound. The phosphine oxide **12** was treated with base (butyllithium) at low temperature in tetrahydrofuran to generate the corresponding phosphinoxy anion, which was allowed to react with the hydroxy-protected ketone **18** [Baggiolini et al., J. Org. Chem. 51, 3098 (1986)] to give the desired 19-nor-vitamin derivative **19**, from which, after protecting-group removal under conventional conditions, there was obtained crystalline 1α,25-dihydroxy-19-norvitamin $D_3$ (**20**).

**Example 1**

(a) (1R,3R,4R,5R) Methyl 3,5-Bis (tert-butyldimethylsilyloxy)-1,4-Dihydroxycyclohexane-Carboxylate (**2**)

p-Toluene sulfonic acid (0.5 g) was added to a solution of quinic acid **1** (12.74 g, 66.3 mmol) in methanol. The solution was stirred for 24 h. Solid NaHCO3 (1.0 g) was added and after 15 min the solution was filtered and concen-

trated to give 12.61 g (62.16 mmol) of the methyl ester in 92% yield.

tert-Butyldimethylsilyl chloride (6.73 g, 44.62 mmol) was added to a solution of methyl (1R,3R,4R,5R) (-)quinate (3.68 g, 17.85 mmol) and triethylamine (6.2 mL, 44.62 mmol) in 44 mL of anhydrous dimethyl formamide at 0°C with stirring. After 4 h the solution was warmed to room temperature and stirring continued for another 14 h. The solution was poured into water and extracted with ether. The combined organic layers were extracted with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 5-10% ethyl acetate in hexane mixtures, to give 4.6 g (60%) of 2 as a white solid. M.p. 82-82.5°C (after recrystallization from hexanes). $^1H$ NMR ($CDCl_3$, 500 MHz) δ 4.53 (bs, 1 H), 4.36 (bs, 1H), 4.11 (ddd, 1H), 3.76 (s, 3H), 3.42 (dd, 1H), 2.31 (bs, 1H), 2.18 bd, 1H), 2.05 (ddd, 2H), 1.82 (dd, 1 H), 0.91 (s 9 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H). MS m/e (relative intensity) 377 (70), 227 (91).

(b) (1R,3R,4R,5R) [3,5-Bis (tert.-butyldimethylsilyloxy)-1,4-dihydroxy]-1-hydroxymethyl cyclohexane (3).

Diisobutyl aluminum hydride (45 mL, 45.0 mmol , 1.0 M in hexanes) was added to a solution of the ester 2 (3.26 g, 7.5 mmol) in ether (45 mL) at -78°C. After 20 min. the solution was warmed to -23°C and stirred for 2 h. The solution was diluted with ether and then 2 N potassium sodium tartrate was slowly added. The solution was warmed to room temperature and stirred for 15 min. The ether layer was separated and the aqueous layer extracted with ether. The combined ether layers were extracted with brine, dried over anh. $MgSO_4$, filtered and concentrated. The material was further purified by column chromatography on silica gel with 25% ethyl acetate/hexanes to give 83% of 3 (2.52 g, 6.20 mmol), Mp. 108-109°C from hexanes. 1H NMR ($CDCl_3$, 500 MHz) δ 4.52 (bs, 1 H), 4.12 (ddd, 1 H) 3.40 (dd, 1 H) (dd, 2 H), 2.28 (d, 1 H) 2.11 (dd, 1 H) 2.00 (ddd, 2 H), 1.52 (dd, 1 H), 1.33 (dd, 1 H) 0.91 (s, 9, H) 2.00 (ddd, 2 H), 1.52 (dd, 1 H), 1.33 (dd, 1 H), 0.91 (s, 3 H), 0.11 (s, 3 H). MS m/e (relative intensity) : 349 (8), 331 (13), 239 (12), 199 (100).

(c) (3R,4R,5R) [3,5-Bis (tert.-butyldimethylsilyloxy)-4-hydroxy]-1-cyclohexanone (4).

Sodium periodate saturated water (28.5 mL) was added to the triol 3 (1.91 g, 4.7 mol) in methanol (124 mL) at 0°C. The solution was stirred for 1 h, then poured into water and extracted with ether. The combined ether fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give 1.72 g (4.59 mmol) of 4 (98%). No further purification was required. Mp. 98-100°C from hexanes. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 4.28 (m, 2 H), 3.80 (bs, 1 H), 2.77 (dd, 1 H, J=14.3, 3.4 Hz), 2.59 (dd, 1H, J=13.1, 10.7 Hz), 2.45 (dd, 1 H, J=14.1, 5.2 Hz) 2.25 (bd, 1 H, J=15.9 Hz), 0.90 (s, 9 H), 0.85 (s, 9H), 0.08 (s, 34 H), 0.08 (s, 3 H), 0.06, (s, 6 H). MS m/e (relative intensity) 317 (62), 231 (16), 185 (76), 143 (100).

(d) (3R,4R,5R) [3,5-Bis(tert.-butyldimethylsilyloxy)-4-trimethylsilyloxy]-1-cyclohexanone (5)

N-(Trimethylsilyl)imidazole (2.52 mL, 26.67 mmol) was added to a solution of the ketoalcohol 4 (1.56 g, 4.167 mmol) in methylene chloride (38 mL). The solution was stirred for 20 h. Water (1 mL) was added and the solution stirred for 30 min. Brine and methylene chloride was added. The brine was extracted with methylene chloride. The combined methylene chloride fractions were dried with anh. $MgSO_4$, filtered and concentrated. The residue was further purified by column chromatography on silica gel with 10% ethyl acetate in hexane to give 5 (1.76 g, 3.95 mmol) in 95% yield. $^1H$ NMR ($CDCl_3$, 500 mHz) δ 4.25 (m,1 H), 4.13 (m, 1, H), 4.04 (m, 1 H), 2.74 (ddd, 2 H), 2.38 (dd, 1 H), 2.19 (dd, 1 H), 0.90 (s, 9 H), 0.86 (s, 9 H), 0.16 (s, 9 H), 0.07 (bs, 12 H). MS m/e (relative intensity): 431 (5), 389 (100), 299 (45), 257 (28).

(e) (3R, 4R, 5R) Ethyl [3,5-bis(tert-butyldimethylsiyloxy)-4-hydroxy]-cyclohexylidene carboxylate. (7).

n.Butyl lithium (1.83 mL, 3.106 mmol) 1.5 M in hexanes was added to a solution of diisopropylamine (0.43 mL, 3.106 mmol) in anhydrous tetrahydrofuran (2.10 mL) under argon at -78°C with stirring. After 15 min. the solution was warmed to 0°C for 15 min. and then cooled to -78°C and ethyl (trimethylsilyl) acetate (0.57 mL, 3.11 mmol) was added. After 15 min. the protected keto compound 5 (0.6934 g, 1.55 mmol) in anhydrous tetrahydrofuran (2.1 + 1.0 mL) was added. The solution was stirred for 2 h at -78°C. Water and additional ether were added. The water was extracted with ether and the combined ether fractions were extracted with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue (the protected ester 6) was dissolved in tetrahydrofuran (5 mL), acetic acid (5 mL), and water (1 mL) were added. The solution was stirred for 72 h, then diluted with ether. Saturated sodium bicarbonate was slowly added until no more carbon dioxide evolution was evident. The ether was separated and the bicarbonate solution extracted with ether. The combined ether fractions were extracted with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The product was further purified by column chromatography, and eluted with ethyl acetate-hexane mixtures (10% to 25% ethylacetate in hexane) to give in 86% yield (two steps) 7. (0.544 g, 1.135 mmol) MS m/e (relative intensity) 429 (4), 399 (6), 387 (100), 341

(f) (3R,4R,5R) Ethyl[3,5-Bis(tert.-butyldimethylsilyloxy)-4-imidazolyl-thiocarbonyloxy-]cyclohexylidenecarboxylate (8).

1,1-thiocarbonyldiimidazole (0.131 g, 0.735 mmol) was added to a solution of the hydroxy ester 7 (0.163 g, 0.37 mmol) in methylene chloride (1.64 mL). The solution was stirred for 60 h. Silica gel was added and the solution concentrated. The residue was added to a column of silica gel and the material eluted with 25% ethyl acetate in hexane to obtain 8 in 87% yield (0.178 g, 0.32 mmol).

(g) (3R,5R) Ethyl [3,5-Bis-(tert.-butyldimethylsilyloxy)]-cyclohexylidene carboxylate (9)

Tributyltin hydride (0.72 mL, 2.66 mmol) was added to a solution of AIBN (17 mg), and the thionoimidazole 8 (0.59 g, 1.06 mmol) in degased toluene (106 mL). The solution was heated with stirring to 100°C for 2 h and then concentrated. The residue was further purified by column chromatography on silica gel eluting with hexane, following with 3% and 25% ethyl acetate in hexane to obtain 0.322 g (0.75 mmol) 9 in 71% yield.

$^1$H NMR ($CDCl_3$, 500 MHz) δ 5.70 (s, 1 H), 4.13 (m, 4 H), 3.05 (dd, J=6.74, 6.16 Hz 1 H), 2.78 (dd, J=6.96, 2.75 Hz, 1 H), 2.38 (dd, J=6.51, 3.25 Hz, 1 H) 2.15 (dd, J=7.74, 6.48 Hz, 1 H) 1.80 (m, 1 H), 1.70 (m, 1 H), 1.26 (t, J=7.29 Hz, 3 H), 0.87 (s, 9 H), 0.85 (s, 9 H), 0.04 (s, 12 H). MS m/e (relative intensity) : 413 (14), 371 (100), 213 (23).

(h) (3R, 5R) [3,5-Bis(tert.-butyldimethylsilyloxy)-cyclohexylidene] ethanol (10)

A solution of 96mg ester 9 (0.22 mmol) in 2 mL of anhydrous toluene was treated at -78°C under argon with 0.62 mL (0.92 mmol) of a 1.5 M solution of diisobutylaluminum hydride in toluene. After the addition, stirring was continued for 1 h at -78°C. The reaction mixture was then quenched by the addition of 2N potassium sodium tartrate, the organic phase was separated, and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with water and brine and dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by fast filtration through a silica gel column, using hexane, followed by hexane-ethyl acetate (10:1) as eluent, to give 58 mg (68%) alcohol 10 as a white solid.

$^1$H NMR (500 MHz) δ 0.06 (br s, 12 H), 0.87 (s, 18 H), 1.80 (m, 1 H), 2.05 (dd, 1 H), 2.18 (br dd J=13, 11 Hz, 1 H), 2.34 (m, 1 H), 4.02 (m, 2 H), 4.13 (m, 2 H), 5.60 (br t, J=7.08 1 H). MS m/e (relative intensity) 237 (85), 211 (83), 171 (100).

(i) (3R,5R)[3,5-Bis(tert.-butyldimethylsilyloxy)-cyclohexylidene]-1-chloroethane (11)

A solution of 50mg (0.37 mmol) N-chlorosuccinimide in 2 mL of anhydrous dichloromethane was treated at 0°C under argon with 30 µL (0.41 mmol) dimethyl sulfide. A white precipitate formed. The mixture was stirred an additional 15 min. at 0°C, then cooled to -25°C and treated with 50 mg (0.13 mmol) of the alcohol 10 dissolved in 0.5 mL of anhydrous dichloromethane. The mixture was stirred under argon for 30 min. at -20°C and then at 0°C for 30 min. The reaction mixture was poured on ice, and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ filtered and evaporated. The residue was purified by fast filtration through a silica gel column, eluting with 5% ethyl acetate in hexane to give 52 mg (quant) of the chloro compound 11. $^1$H NMR ($CDCl_3$ 500 MHz), δ 0.06 (s, 12 H), 0.89 (s, 18 H), 1.73 (br dd, 1 H), 2.22 (m, 1 H) 2.30 (m, 1 H), 2.32 (m, 1 H), 4.04 (dd, J=7.3, 10.8 Hz, 2 H), 4.11 (dd, J=2.87, 10.46 Hz, 2 H), 5.51 (br t 1 H). MS m/e (relative intensity) : 237 (93), 215 (52), 189 (79), 105 (100).

(j) (3R,5R)-[Bis(tert.-butyldimethylsilyloxy)-cyclohexyli-denelethyl-diphenylphosphine oxide (12).

40 µL (60 µmol) n.Butyl lithium (1.5 M in hexanes) was added to 10 µL (60 µmol) diphenylphosphine in 30 µL anhydrous tetrahydrofuran at 0°C with stirring under argon. The orange solution was treated at 0°C with 20 mg (50 µmol) of the allylic chloride 11 in 300 + 200 µL anhydrous tetrahydrofuran. The resulting yellow solution was stirred an additional 40 min at 0°C and quenched by the addition of water. Solvents were evaporated under reduced pressure and the residue was dissolved in chloroform. The chloroform layer was shaken twice with 5% hydrogen peroxide. The chloroform layer was separated and washed with aqueous sodium sulfite, water and brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was dissolved in 20% 2-propanol in hexane and passed through a silica SepPak and purified by HPLC (Zorbax-Sil 9.4 x 25 cm column, 20% 2-propanol in hexane) to give 5.5 mg (22%) of the phosphine oxide 12.

UV (EtOH):$\lambda_{max}$258,265,272 nm, $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.01 (ms, 12 H), 0.85 (m s, 18 H) 1.65 (m, 2 H), 1.91 (m, 1 H) 2.00 (m, 1 H), 2.22 (br d J=3.2 Hz 1 H), 3.05 (dt, J=8.5, 14.9 Hz, 1 H) 3.14 (dt, J=8.5, 14.9 Hz, 1 H), 3.98 (br s 1 H), 5.28 (q, 1 H), 7.46 (m, Ar-5 H), 7.73 (m, Ar-5 H). MS m/e (relative intensity) : 570 (M+, 1) 513 (100), 381 (46), 306 (20), 202 (55), 75 (20).

**Example 2**

(a) (1R,3R,4R,5R) Methyl [3,5-Bis(tert.-butyldimethylsilyloxy)1-hydroxy-4-imidaz olylthiocarbonyloxy-cyclohexanone carboxylate (**13**)

1,1'-Thiocarbonyldiimidazole (0.7 g, 4.0 mmol) was added to a solution of the 1,3-protected methyl quinate **2** (1.1 g, 2.5 mmol) in methylene chloride (10 mL). The solution was stirred at RT for 70 h. The solution was concentrated and purified by column chromatography on silica gel and the product eluted with hexane ethyl acetate mixtures to give **13** (1.2 g, 90%). $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.14 (s, 3H), 0.77 (s, 9H), 0.91 (s, 9H), 2.03 (m, 2H), 2.28 (m, 2H), 3.80 (s, 3H), 4.43 (br, s, 1H), 4.58 (m, 1H), 4.66 (br, s, 1H), 5.52 (dd, 1H, J=2.71, 9.05 Hz), 7.06 (d, 1H, J=1.49 Hz), 7.64 (d, 1H, J=2.76 Hz), 8.38 (s, 1H).

(b) (1R,3R,5R) Methyl [3,5-Bis(tert.-butyldimethylsilyloxy)-1-hydroxycyclohexane carboxylate (**14**)

Tributyltin hydride (0.72 mL, 2.66 mmol) was added to a solution of AIBN (17 mg), and the thionoimidazole **13** (0.58 g, 1.06 mmol) in degased toluene (106 mL). The solution was heated with stirring to 100°C for 2 h and then concentrated. The residue was further purified by column chromatography on silica gel eluting with hexane, followed with 3% and 25% ethyl acetate in hexane to obtain **14** (0.322 g, 71%). $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.14 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 0.91 (s, 9 H), 1.46 (m, 2H), 1.56 (m, 1H), 1.82 (dd, 1H), 2.42 (d, J=12.21 Hz), 2.51 (d, J=13.39 Hz), 3.69 (s, 3H), 4.17 (br, s, 1H), 4.25 (m, 1H).

(c) (1R,3R,5R)-[3,5-Bis(tert.-butyldimethylsilyoxy)-1-hydroxy-1-hydroxymethylcyclohexane (**15**)

Diisobutyl aluminum hydride (6 mL, 9 mmol, 1.5 M in toluene) was added to a solution of the ester **14** (0.56 g, 1.3 mmol) in anhydrous toluene (20 mL) at -78°C. After 20 min the solution was warmed to 0°C and stirred for 1 h. The solution was slowly quenched by adding to a stirred 0°C solution of 2N potassium sodium tartrate. Ethyl acetate was added and the organic layer separated and the water phase extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The material was further purified by column chromatography on silica gel with ethyl acetate hexane mixtures to give the diol **15** (0.3 g, 59%) $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.14 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 1.28 (dd, 1H), 1.43 (dd, 1H), 2.00 (ddd 3H), 2.16 (dd, 1H), 3.33 (dd, 1H), 3.40 (dd, 1H), 4.34 (m, 2x 1H).

(d) (3R, 5R) [3,5-Bis(tert.-butyldimethylsilyloxy)]-1-cylohexanone (**16**)

Sodium periodate saturated water (28.5 mL) was added to the diol **15** (1.8 g, 4.7 mmol) in methanol (124 mL) at 0°C. The solution was stirred for 1 h, then poured into water and extracted with ether. The combined ether fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give **16** (1.5 g, 90%). No further purification was required. $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.14 (s, 3H), 0.15 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 1.94 (m, 2H), 2.35 (m, 2H), 2.54 (m, 2H), 4.35 (m, 2 x 1 H).

(3R,5R) Ethyl [3,5-bis(tert.-butyl-dimethylsilyloxy)-cyclohexylidene carboxylate (**9**).

n.-Butyl lithium (1.83 mL, 3.106 mmol) 1.5 M in hexanes was added to a solution of diisopropylamine (0.43 mL, 3.106 mmol) in anhydrous tetrahydrofuran (2.10 mL) under argon at -78°C with stirring. After 15 min the solution was warmed to 0°C for 15 min and then cooled to -78°C and ethyl(trimethylsily)acetate (0.57 mL, 3.11 mmol) was added. After 15 min the protected keto compound **16** (0.55 g, 1.55 mmol) in anhydrous tetrahydrofuran (2.1 + 1.0 mL) was added. The solution was stirred for 2 h at -78°C. Water and additional ether were added. The water was extracted with ether and the combined ether fractions were extracted with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The product was further purified by column chromatography, and eluted with ethyl acetate-hexane mixtures to give **9** (0.544 g, 86%). $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 12H), 0.85 (s, 9H), 0.87 (s, 9 H), 1.26 (t, J=7.29 Hz, 3H), 1.70 (m, 1H), 1.80 (m, 1H), 2.15 (dd, J=7.74, 6.48 Hz, 1H), 2.38 (dd, J=6.51, 3.25 Hz, 1H), 2.78 (dd, J=6.96, 2.75 Hz, 1H), 3.05 (dd, J=6.74, 06.16 Hz, 1H), 4.13 (m, 4 H), 5.70 (s, 1H).

**Example 3**

(a) 3,5-Bis(di-butyldimethylsilyoxy)-4-imidazolyl-thiocarbonyl-oxy-1-cyclohexanone (**17**)

Reaction of hydroxy-ketone **4** with 1,1-thiocarbonyldiimidazole, under conditions analogous to those described in

Example 2(a) provides the thiocarbonylimidazole derivatives of structure 17.

(b) 3,5-Bis(tert.-butyldimethylsilyloxy)-1-cyclohexanone (16)

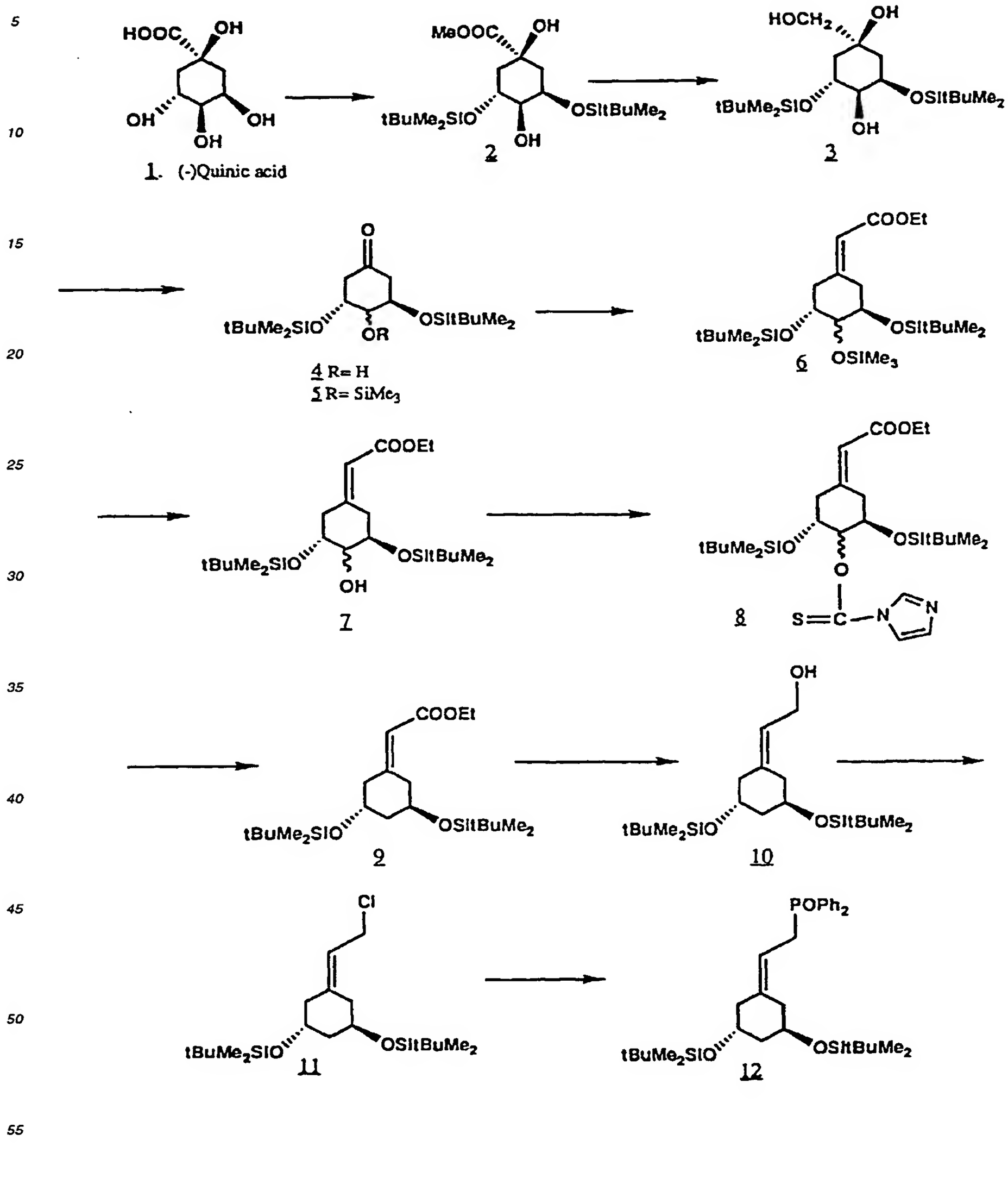
Treatment of compound 17 as obtained in Example 3(a) with tributyltin hydride in the presence of azaisobutyionitrile in toluene, under conditions analogous to those of example 1(g) provides the cyclohexanone derivative 16.

**Example 4**

1α-25-Dihydroxy-19-nor-vitamin $D_3$(15)

5.5 mg (10 µmol) phosphine oxide 12 was dissolved in 200 µL anhydrous tetrahydrofuran, cooled to 0°C and 7 mL (10 µmol) n.butyl lithium (1.5 molar in hexanes) added under argon with stirring. The mixture was cooled to -78°C and 5mg (14 µmol) protected ketone 13 added in 200 µL + 100 µL anhydrous tetrahydrofuran. The mixture was stirred under argon at -78°C for 1 h and then at 0°C for 16 h. 20% Ethyl acetate in hexane was added and the organic phase washed with saturated ammonium chloride solution, 10% NaHCO3 solution, brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was dissolved in 10% ethyl acetate in hexane, passed through a silica SepPak and purified by HPLC in 10% ethyl acetate in hexane (Zorbax Sil 9.4 x 25 cm column) to give 550 µg of the protected 19-nor vitamin $D_3$ 14. This was dissolved in 500 µL anhydrous tetrahydrofuran and treated with 500 µL of a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran. The mixture was stirred under argon at 50°C for 50 min. cooled and extracted with ether. The ether phase was washed with 10% NaHCO3 solution, brine and dried over anhydrous $MgSO_4$, filtered and evaporated. The reside was filtered through a silica SepPak and purified by HPLC (Zorbax Sil 9.4 x 25 cm column, 20% 2-propanol in hexane) to give 100 µg of pure 1α,25-dihydroxy 19-nor-vitamin $D_3$ 15. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 0.52 (3H, s, 18-$CH_3$), 0.92 (3H, d, J=6.9 Hz, 21-$CH_3$), 1.21 (6H, s, 26 & 27-$CH_3$), 4.02 (1H, m, 3α-H), 4.06 (1H, m, 1β-H), 5.83 (1 H, d, J=11.6 Hz, 7-H), 6.29 (1H, d, J=10.7 Hz, 6-H). UV (in EtOH): $\lambda_{max}$: 243, 251.5, 261nm, Mass spectrum m/e (relative intensity) : 404 (M+, 100), 386 (41) 371 (20), 275 (53), 245 (51), 180 (43), 135 (72), 95 (82), 59 (18). UV (EtOH) $\lambda_{max}$: 243, 251.5, 261 (ε 31,300, 34,600, 24,900).

Scheme I.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OH
OH
OH
OH
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MeOOC
OH
tBuMe2SiO
OSitBuMe2
OH
2
HOCH2
OH
tBuMe2SiO
OSitBuMe2
OH
3
O
tBuMe2SiO
OSitBuMe2
OR
4 R= H
5 R= SiMe3
COOEt
tBuMe2SiO
OSitBuMe2
6 OSiMe3
COOEt
tBuMe2SiO
OSitBuMe2
OH
7
COOEt
tBuMe2SiO
OSitBuMe2
O
S=C
N
N
8
COOEt
tBuMe2SiO
OSitBuMe2
9
OH
tBuMe2SiO
OSitBuMe2
10
Cl
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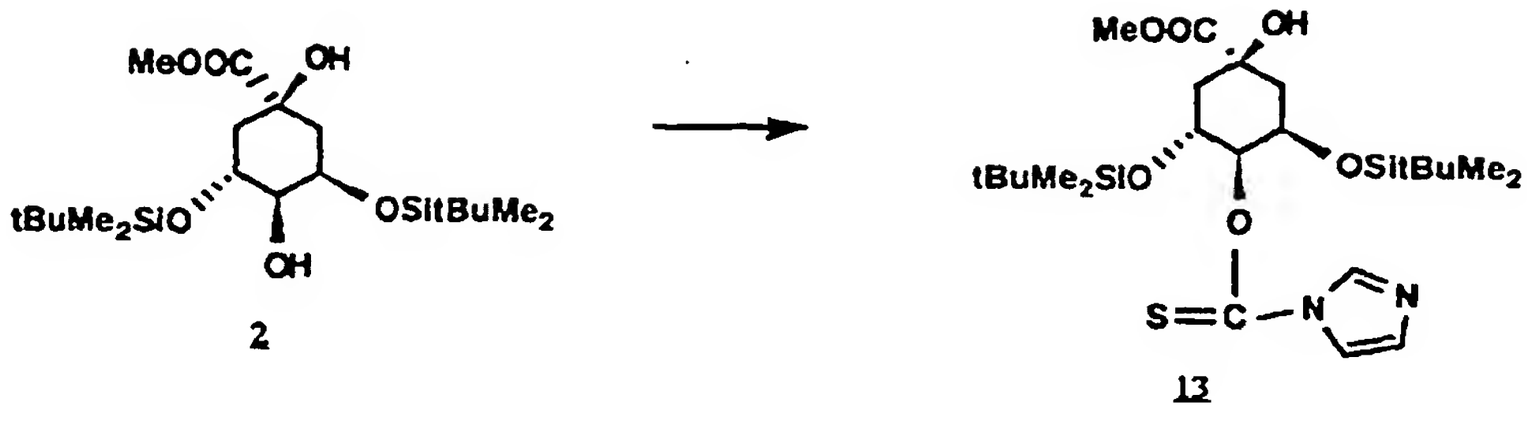
OSitBuMe2
11
POPh2
tBuMe2SiO
OSitBuMe2
12

Scheme II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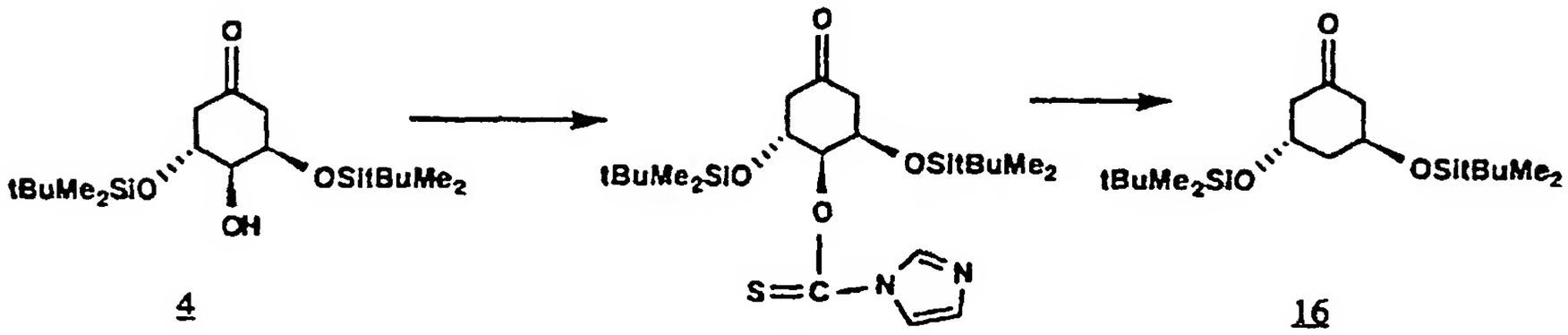
OSitBuMe2
OH
2
13
14
15
16
9
HOCH2
O
COOEt
S=C
N

Scheme III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OSitBuMe2
OH
4
O
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N
N
17
O
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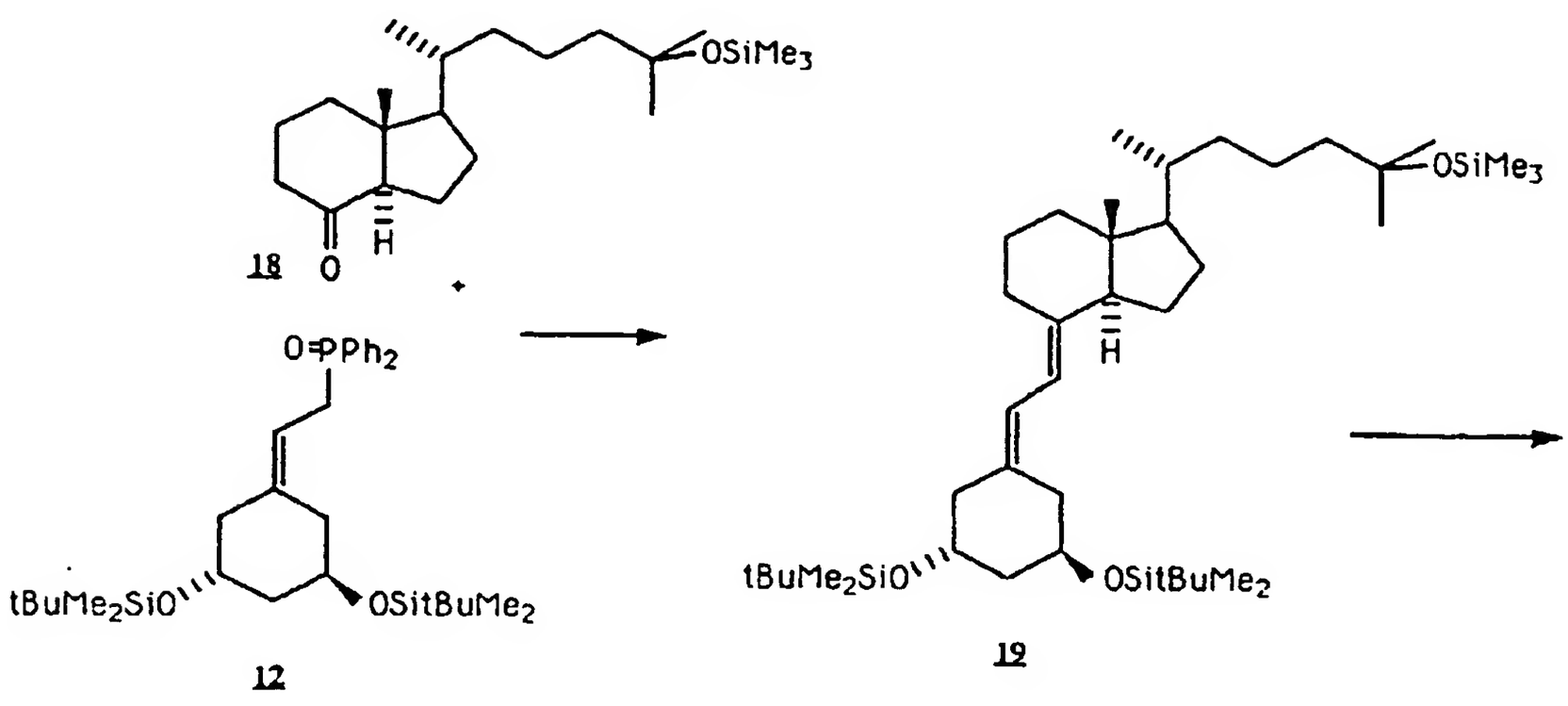
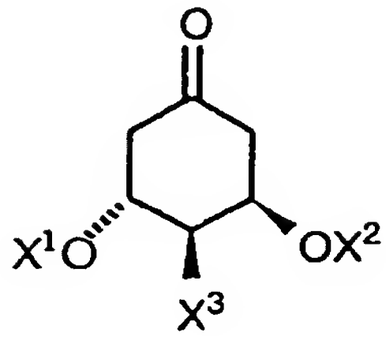
OSitBuMe2
16

Scheme IV

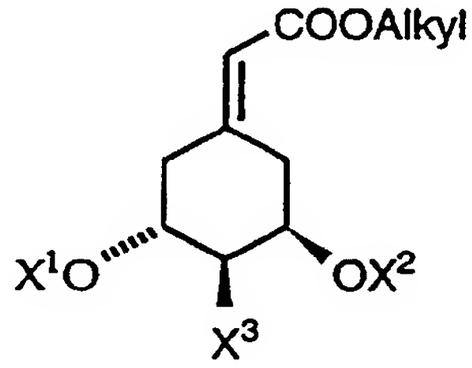



## Claims

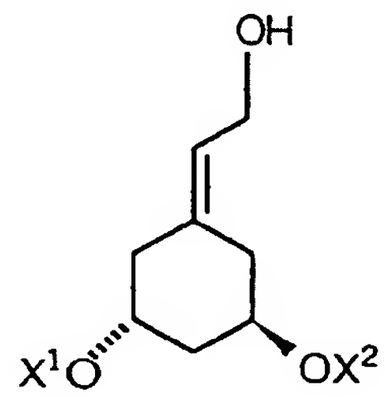
1. A method of making a 19-nor vitamin D compound which comprises the steps of condensing a ketone of the structure:



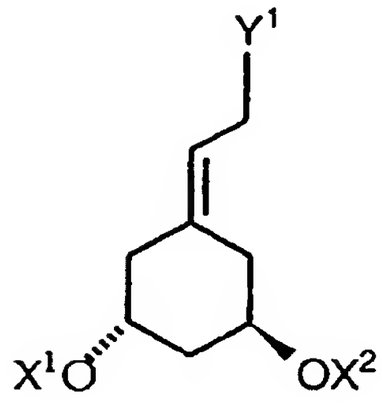
where $X^1$ and $X^2$ are each a hydroxy-protecting group, and $X^3$ is hydrogen or hydroxy, in the presence of a strong base to obtain an ester having the structure:



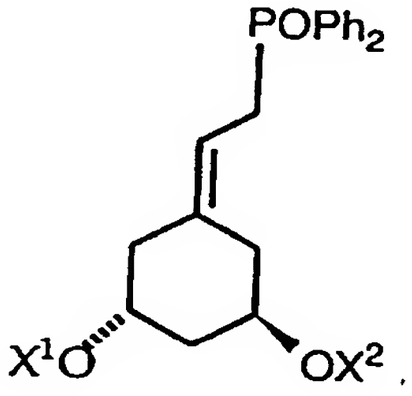
where $X^1$, $X^2$ and $X^3$ are as defined above, and "Alkyl" represents a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, with the proviso that when $X^3$ in the above ketone is a hydroxy function, that hydroxy function be first protected with a hydroxy-protecting group prior to the base-promoted condensation reaction, reducing said ester to obtain the allylic alcohol having the structure:



where $X^1$ and $X^2$ are as defined above, with the proviso that if $X^3$ in the above ester is a protected hydroxy function that function is removed by removing the protecting group and converting the resulting free alcohol to a thions ester derivative which is subjected to a reductive free radical deoxygenation reaction converting said allylic alcohol to a derivative having the structure:

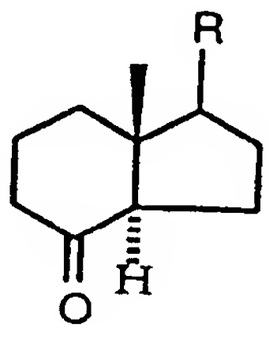


where $Y^1$ is halogen, which is I, Br or Cl, or an O-tosyl or O-mesyl group, and where $X^1$ and $X^2$, which may be the same or different, are hydroxy-protecting groups, converting said derivative to the phosphine oxide:

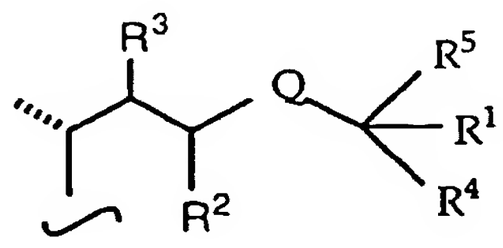


where $X^1$ and $X^2$ are as defined above by treatment of said derivative with a metal diphenylphosphide and a subsequent peroxide oxidation:

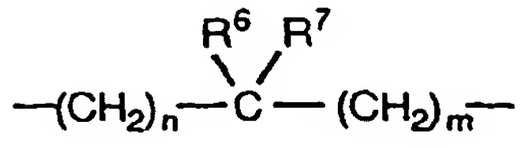
reacting the phosphine oxide with a ketone of the structure:



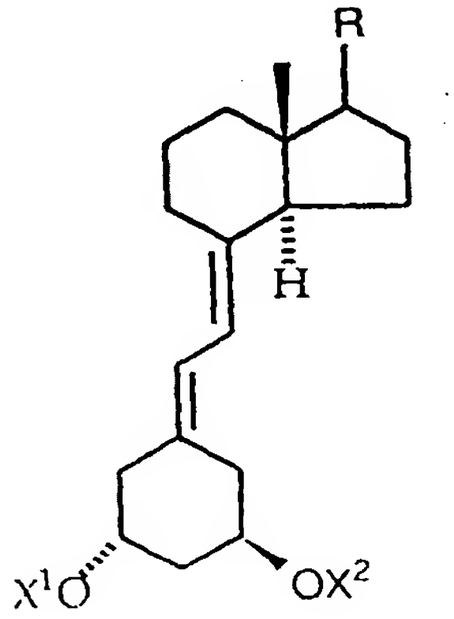
where R is hydrogen, alkyl, hydroxyalkyl, deuteralkyl, fluoroalkyl, the alkyl groups of which being as defined for "Alkyl" as defined above or a side chain of the formula:



where each of $R^1$, $R^2$ and $R^3$, which may be the same or different, is hydrogen, hydroxy, protected hydroxy, or alkyl, said alkyl represents a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, where the bond between carbons 22 and 23 may be a single, double or triple bond, Q is the group:



where each of $R^6$ and $R^7$, which may be the same or different, is hydrogen, alkyl, hydroxyalkyl, hydroxy, protected hydroxy or fluoro, said hydroxyalkyl represents an alkyl radical substituted by one or more hydroxy groups, or $R^6$ and $R^7$ taken together represent an oxo group or an alkylidene group, and each of n and m, which may be the same or different, is 0, 1, 2, 3, 4 or 5, each of $R^4$ and $R^5$, which may be the same or different, is fluoroalkyl or the group Q-H, or $R^4$ and $R^5$ taken together, represent the group Q, with the proviso that when $R^4$ and $R^5$ taken together are Q at least one of n or m is 1 or more, and wherein any of the CH-groups at positions 20, 22 or 23 in the side chain may be replaced by a nitrogen atom, or wherein any of the groups $-CH(CH_3)-$, $CH(R^3)-$, or $-CH(R^2)-$ at positions 20, 22 and 23, respectively, may be replaced by an oxygen or sulfur atom, to produce a 19-nor-vitamin D compound of the structure:

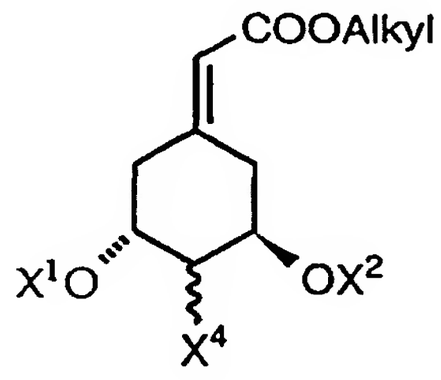


where $X^1$, $X^2$ and R are as defined above, and subsequently, if desired, removing one or more hydroxy-protecting groups.

2. A method according to claim 1 wherein the hydroxy-protecting groups are removed by subjecting the hydroxy-protected 19-nor vitamin D compound to hydrolysis or hydride reduction.

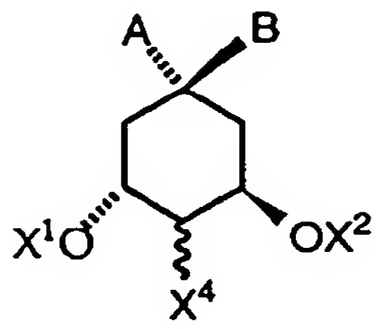
3. A method according to claim 1 or 2 for producing 19-nor-1α,25-dihydroxyvitamin $D_3$ or 19-nor-1α-hydroxyvitamin $D_3$.

4. A compound of the structure:



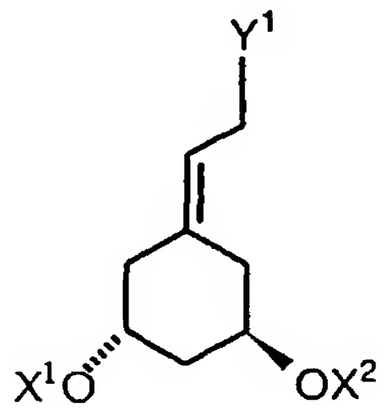
where each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group, $X^4$ is hydrogen, hydroxy or protected hydroxy, and "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form.

5. A compound of the structure:



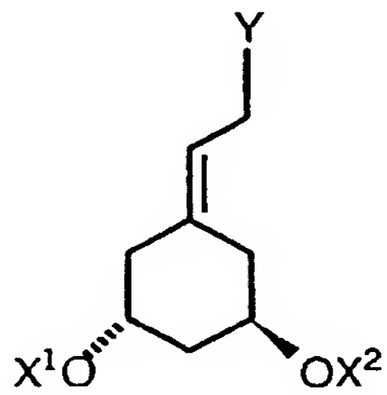

where each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group, $X^4$ is hydrogen, and A is -COOAlkyl or -$CH_2$ OH, where "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, and B is hydroxy or A and B together represent an oxo group.

6. A compound of the structure:




where each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group and $Y^1$ is hydroxy, protected-hydroxy, O-tosyl, O-mesyl, bromine, chlorine or iodine.

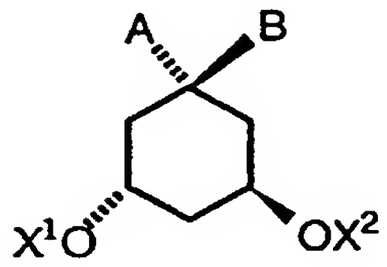
7. A compound of the structure:



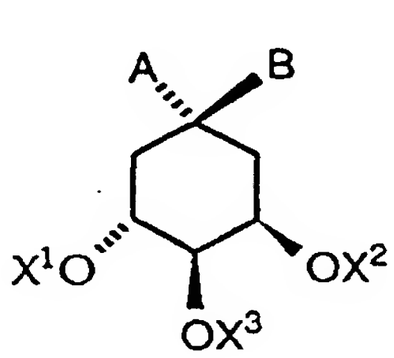

where each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group, and where Y is -$POPh_2$, or -$PO(OAlkyl)_2$, or -$SO_2Ar$, or -$Si(Alkyl)_3$, said Ar representing a phenyl, or an alkylnitro- or halo-substituted phenyl, and said alkyl is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form.

8. A compound according to claim 7 wherein Y is -$POPh_2$.

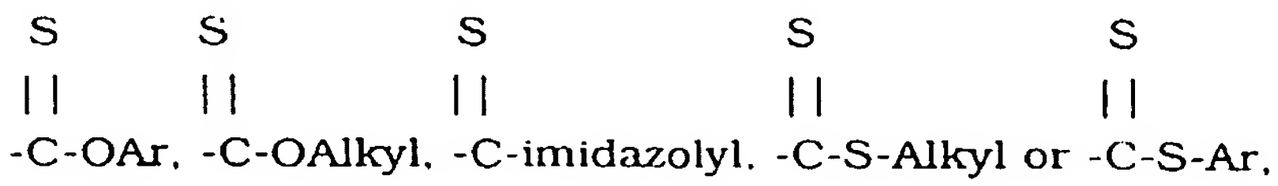
9. A process for making a compound of the formula:



wherein $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group, A is -COOAlkyl or $-CH_2OH$ and B is hydroxy, or A and B together represent either oxo or =CHCOOAlkyl, where "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, which comprises eliminating the group in the 4-position in a compound of the formula:

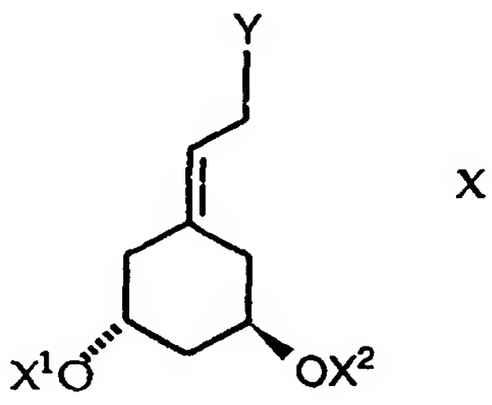


where $X^3$ is



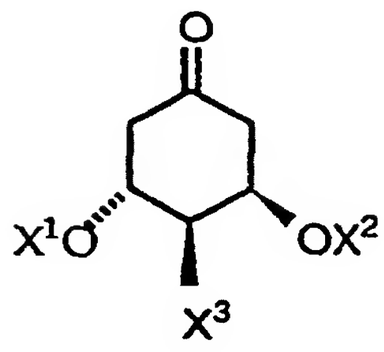
said Ar representing a phenyl, or an alkyl-, nitro-, or halo-substituted phenyl, and said alkyl is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form by subjecting said compound to a reductive free radical deoxygenation reaction.

**10.** A method of making a compound of the formula X:

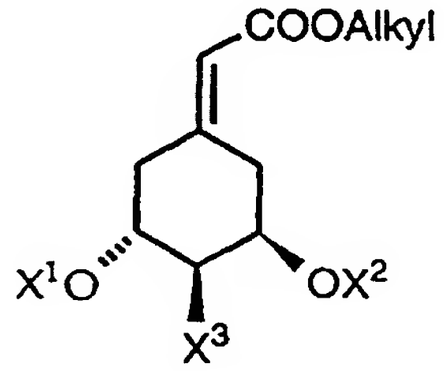


X

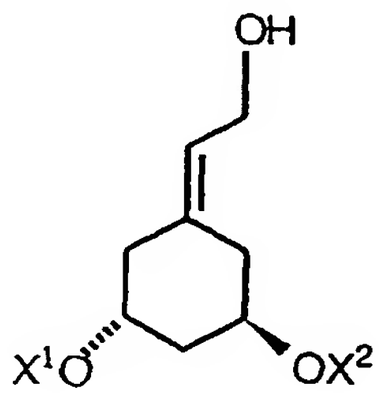
wherein each of $X^1$ and $X^2$, which may be the same or different is hydrogen or a hydroxy-protecting group and Y is hydroxy, halogen, O-mesyl, O-tosyl or a hydroxy-protecting group, which comprises condensing a ketone of the structure:



where each of $X^1$ and $X^2$, which may be the same or different, is a hydroxy-protecting group, and $X^3$ is hydrogen or hydroxy, in the presence of a strong base to produce an ester of the formula:

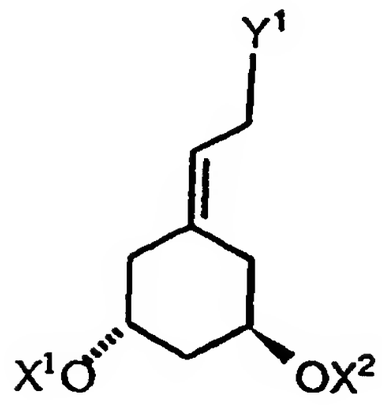


where $X^1$, $X^2$ and $X^3$ are as defined above, and "Alkyl" represents a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form, with the proviso that when $X^3$ in the above ketone is a hydroxy function, that hydroxy function be first protected with a hydroxy-protecting group prior to the base-promoted condensation reaction, reducing said ester to produce an alcohol of the formula:



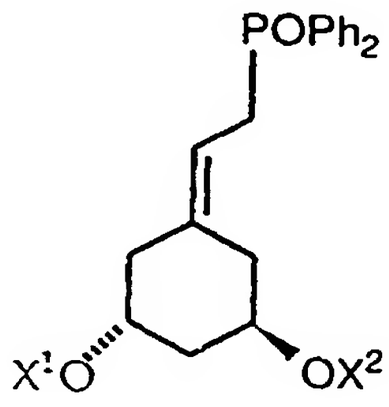
where $X^1$ and $X^2$ are as defined above, and optionally converting said alcohol to its corresponding halogen, O-tosyl, O-mesyl or hydroxy-protected derivative and optionally removing the hydroxy protecting groups $X^1$ and $X^2$, with the proviso that if $X^3$ in the above ester is a protected hydroxy function, that function is eliminated prior to the reduction reaction by removing the protecting group and subjecting the thiono-ester derivative of the alcohol to a reductive free radical deoxygenation reaction.

11. The method of claim 10 further including the step of converting a compound of formula X to:

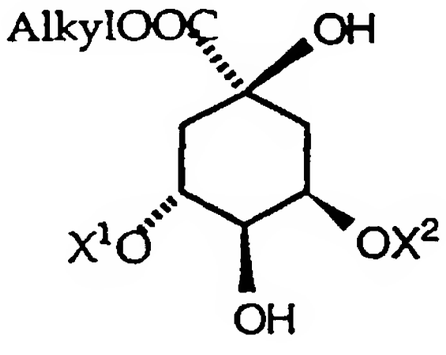


wherein each of $X^1$ and $X^2$, which may be the same or different is hydrogen or a hydroxy-protecting group and $Y^1$ is $-POPh_2$, $-Si(Alkyl)_3$, $-PO(OAlkyl)_2$, or $-SO_2Ar$, said Ar representing a phenyl or an alkyl-, nitro-, or halo-substituted phenyl, and said alkyl is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form.

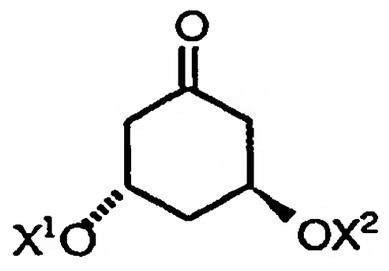
**12.** The method of claim 10 for making a phosphine oxide of the formula:



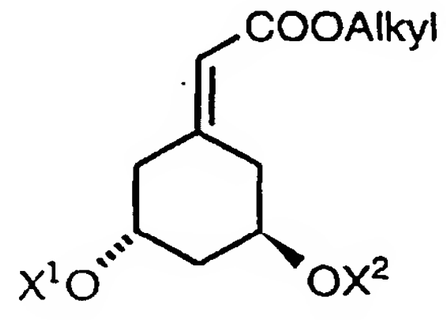
wherein each of $X^1$ and $X^2$, which may be the same or different, is hydrogen or a hydroxy-protecting group which comprises eliminating the 4-hydroxyl group of a quinic acid of the formula:



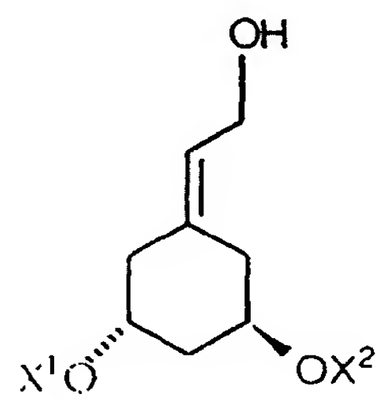
where each of $X^1$ and $X^2$, which may be the same or different is a hydroxy-protecting group and "alkyl" is a straight-chain or branched saturated hydrocarbon radical of 1 to 10 carbons in any isomeric form by treating the corresponding thiono-ester with a hydrogen radical source in the presence of a radical initiator, converting the resulting dehydroxylated compound to a ketone of the formula:



wherein $X^1$ and $X^2$ are as defined above, by treating the deoxygenated compound with a hydride reducing agent followed by oxidative cleavage of the resulting vicinal diol, condensing the ketone in the presence of alkyl (trimethylsilyl) acetate and a strong base to produce an ester of the formula:



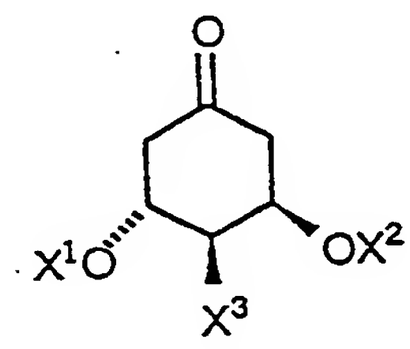

wherein $X^1$ and $X^2$, and "alkyl" are as defined above, reducing said ester to produce an alcohol of the formula:



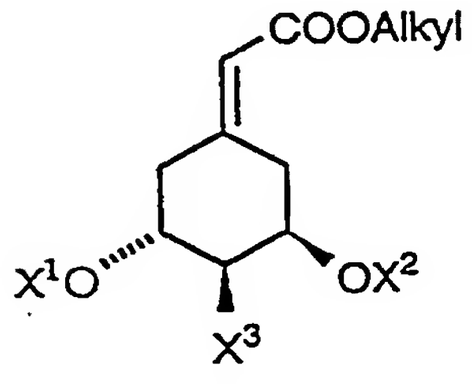

wherein $X^1$ and $X^2$ are as defined above, and converting said alcohol to the corresponding allylic chloride or tosylate and thereafter displacing the chloride or tosylate group with diphenyl phosphide and oxidizing the resulting diphenyl phosphine derivative to the phosphine oxide and, optionally, removing the hydroxy protecting groups.

**Patentansprüche**

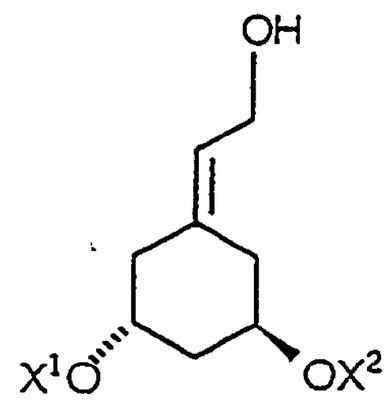
1. Verfahren zur Herstellung einer 19-Norvitamin D-Verbindung, das die Stufen umfaßt: Kondensieren eines Ketons der Struktur:



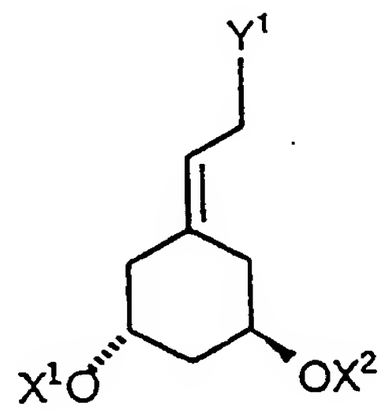

worin jeder der Reste $X^1$ und $X^2$ eine Hydroxy-Schutzgruppe ist, und $X^3$ Wasserstoff oder Hydroxy ist, in Gegenwart einer starken Base, unter Erhalt eines Esters der Struktur:



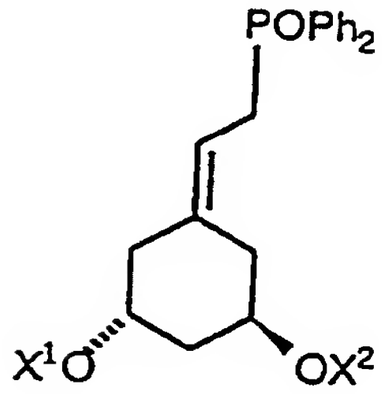

worin $X^1$, $X^2$ und $X^3$ die vorstehend angegebene Bedeutung besitzen und "Alkyl" ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form bedeutet, mit der Maßgabe, daß, wenn $X^3$ im vorstehenden Keton eine Hydroxyfunktion ist, diese Hydroxyfunktion vor der durch Base geförderten Kondensationsreaktion mit einer Hydroxyschutzgruppe geschützt wird, Reduzieren des Esters unter Erhalt des Allylalkohols der Struktur:




worin $X^1$ und $X^2$ die vorstehend angegebene Bedeutung besitzen, mit der Maßgabe, daß, wenn $X^3$ im obigen Ester eine geschützte Hydroxyfunktion ist, diese Funktion entfernt wird durch Entfernen der Schutzgruppe und Überführen des resultierenden freien Alkohols in ein Thionoesterderivat, das einer reduktiven freien radikalischen Deoxygenierungsreaktion unterworfen wird, Überführen des Allylalkohols in ein Derivat der Struktur:

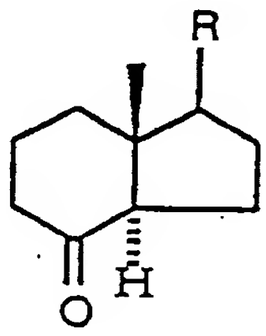



worin $Y^1$ Halogen, das I, Br oder Cl ist, oder eine O-Tosyl- oder O-Mesyl-Gruppe bedeutet, und worin $X^1$ und $X^2$, die gleich oder verschieden sein können, Hydroxyschutzgruppen sind, Überführen des Derivats in das Phosphinoxid:

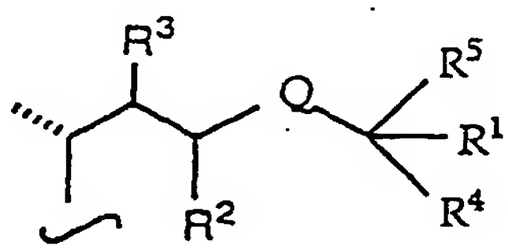


worin $X^1$ und $X^2$ die vorstehend angegebene Bedeutung besitzen, durch Behandeln des Derivats mit einem Metalldiphenylphosphid und nachfolgende Peroxidoxidation;

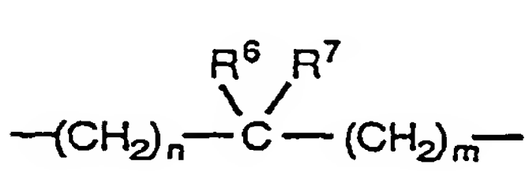
Umsetzenlassen des Phosphinoxids mit einem Keton der Struktur:



worin R Wasserstoff, Alkyl, Hydroxyalkyl, Deuteroalkyl, Fluoralkyl, worin die Alkylgruppen die vorstehend für "Alkyl" angegebene Bedeutung besitzen, oder eine Seitenkette der Formel:

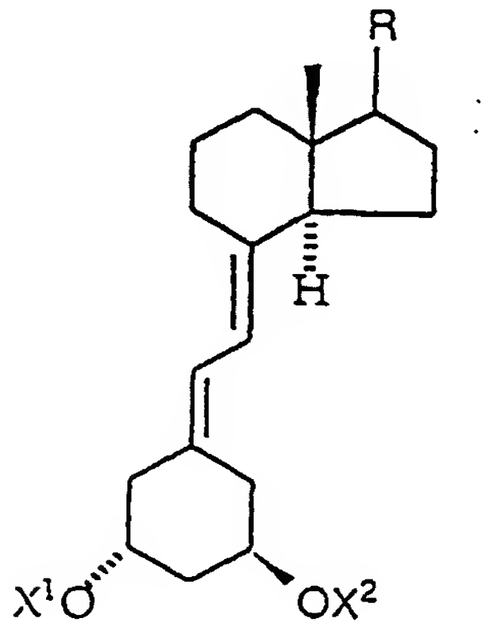


worin jeder der Reste $R^1$, $R^2$ und $R^3$, die gleich oder verschieden sein können, Wasserstoff, Hydroxy, geschütztes Hydroxy, oder Alkyl bedeuten, und wobei das Alkyl ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form darstellt, wobei die Bindung zwischen den Kohlenstoffatomen 22 und 23 eine Einfach-, Doppel- oder Dreifachbindung sein kann, Q die Gruppe ist:



worin jeder der Reste $R^6$ und $R^7$, die gleich oder verschieden sein können, Wasserstoff, Alkyl, Hydroxyalkyl, Hydroxy, geschütztes Hydroxy oder Fluor bedeuten, und das Hydroxyalkyl ein mit einer oder mit mehreren Hydroxygruppen substituiertes Alkylradikal darstellt, oder $R^6$ und $R^7$ zusammen eine Oxogruppe oder eine Alkylidengruppe bedeuten, und n und m, die gleich oder verschieden sein können, 0, 1, 2, 3, 4 oder 5 sind, jeder der Reste $R^4$ und $R^5$, die gleich oder verschieden sein können, Fluoralkyl oder die Gruppe QH bedeuten, oder $R^4$ und $R^5$ zusammengenommen eine Gruppe Q bedeuten, mit der Maßgabe, daß, wenn $R^4$ und $R^5$ zusammen Q sind, mindestens eine der Bedeutungen n oder m 1 oder mehr ist, und worin irgendeine der CH-Gruppen in den Stellungen 20, 22 oder 23 in der Seitenkette durch ein Stickstoffatom ersetzt sein kann, oder worin irgendeine der Gruppen -$CH(CH_3)$-, $CH(R^3)$- oder -$CH(R^2)$- in den Stellungen 20, 22 bzw. 23 durch ein Sauerstoff- oder Schwefelatom ersetzt

sein kann, um eine 19-Norvitamin D-Verbindung der Struktur herzustellen:

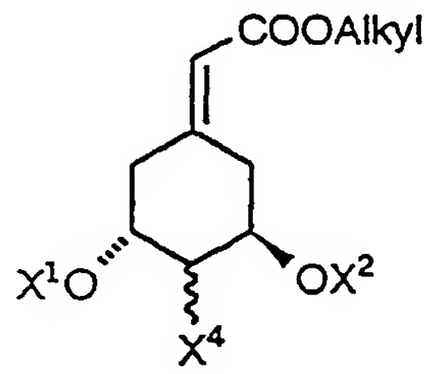


worin $X^1$, $X^2$ und R die vorstehend angegebene Bedeutung besitzen, und danach, wenn erwünscht, eine oder mehrere Hydroxyschutzgruppen entfernt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Hydroxyschutzgruppen entfernt werden, indem man die Hydroxy-geschützte 19-Norvitamin D-Verbindung einer Hydrolyse oder Hydridreduktion unterwirft.

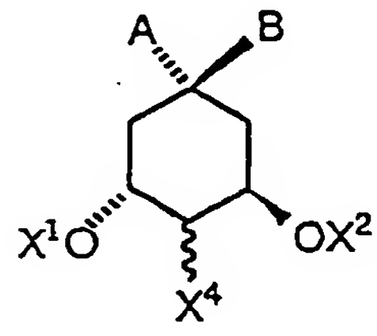
3. Verfahren nach Anspruch 1 oder 2 zur Herstellung von 19-Nor-1α,25-dihydroxyvitamin $D_3$ oder 19-Nor-1α-hydroxyvitamin $D_3$.

4. Verbindung der Struktur:



worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutzgruppe ist, $X^4$ Wasserstoff, Hydroxy oder geschütztes Hydroxy ist, und "Alkyl" ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form ist.

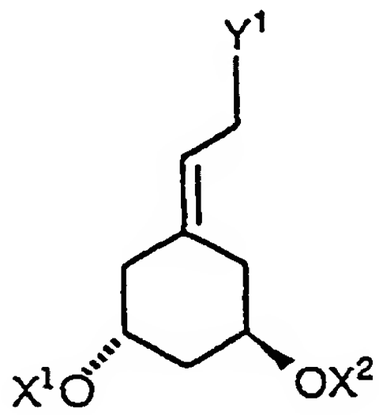
5. Verbindung der Struktur:



worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutz-

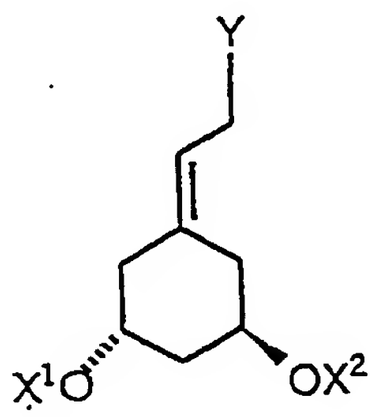
gruppe ist, $X^4$ Wasserstoff ist, und A -COOAlkyl oder $-CH_2OH$ ist, worin "Alkyl" ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form ist, und B Hydroxy ist oder A und B zusammen eine Oxogruppe bedeuten.

6. Verbindung der Struktur:



worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutzgruppe ist, und $Y^1$ Hydroxy, geschütztes Hydroxy, O-Tosyl, O-Mesyl, Brom, Chlor oder Jod ist.

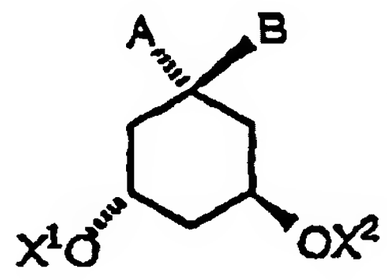
7. Verbindung der Struktur:



worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutzgruppe ist, und worin Y $-POPh_2$, oder $-PO(OAlkyl)_2$ oder $-SO_2Ar$ oder $-Si(Alkyl)_3$ ist, und Ar Phenyl, oder ein Alkyl, Nitro- oder Halogen-substituiertes Phenyl ist, und Alkyl ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form ist.

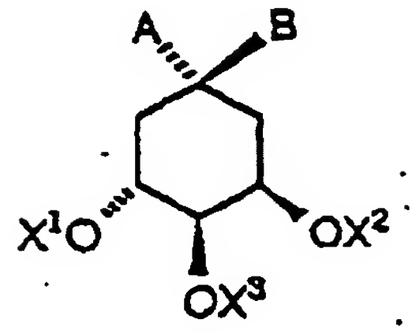
8. Verbindung nach Anspruch 7, dadurch gekennzeichnet, daß Y = $-POPh_2$.

9. Verfahren zur Herstellung einer Verbindung der Formel



worin $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutzgruppe bedeuten, A -COOAlkyl oder $-CH_2OH$ bedeutet, und B Hydroxy ist, oder A und B zusammen entweder Ooxo oder =CHCOO-Alkyl bedeuten, worin "Alkyl" ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form ist, dadurch gekennzeichnet, daß man die Gruppe in 4-Stellung

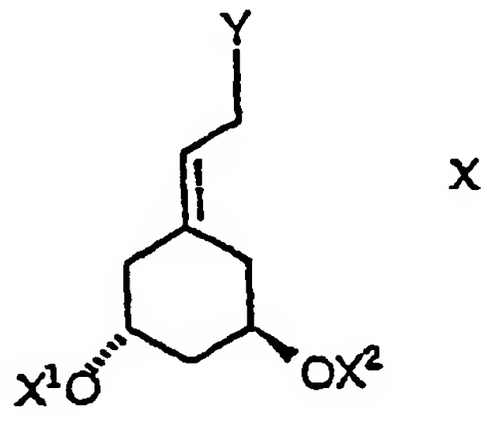
einer Verbindung der Formel:



worin $X^3$

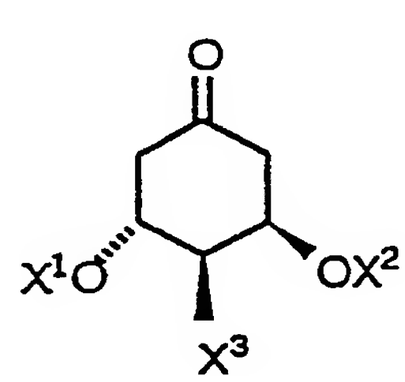
ist, wobei Ar Phenyl, oder ein Alkyl-, Nitro- oder Halogen-substituiertes Phenyl darstellt, und Alkyl ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form ist, eliminiert, indem man die verbindung einer reduktiven freien radikalischen Deoxygenierungsreaktion unterwirft.

**10.** Verfahren zur Herstellung einer Verbindung der Formel X:

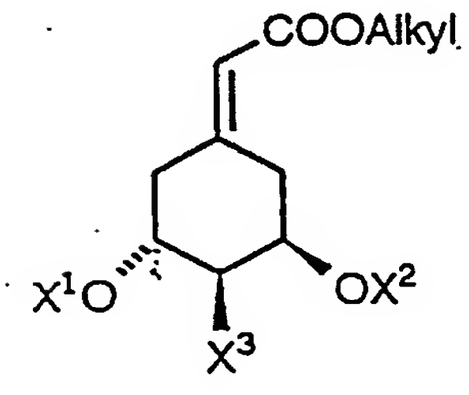


X

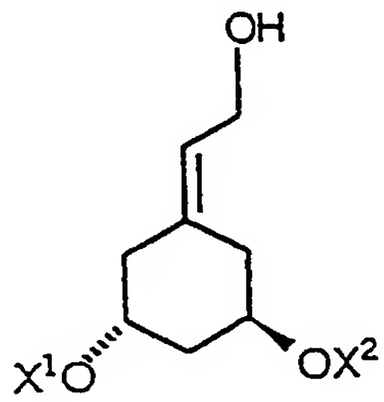
worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutzgruppe bedeutet und Y Hydroxy, Halogen, O-Mesyl, O-Tosyl oder eine Hydroxy-Schutzgruppe ist, dadurch gekennzeichnet, daß man ein Keton der Struktur:



worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, eine Hydroxy-Schutzgruppe ist, und $X^3$ Wasserstoff oder Hydroxy ist, in Gegenwart eines starken Base kondensiert unter Herstellung eines Esters der Formel:

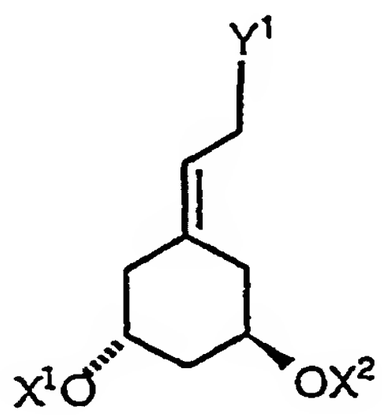



worin $X^1$, $X^2$ und $X^3$ die vorstehend angegebene Bedeutung besitzen, und "Alkyl" ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomerenr Form bedeutet, mit der Maßgabe, daß, wenn $X^3$ in obigem Keton eine Hydroxyfunktion ist, diese Hydroxyfunktion vor der durch die Base geförderten Kondensationsreaktion mit einer Hydroxy-Schutzgruppe geschützt wird, Reduzieren des Esters zur Herstellung eines Alkohls der Formel:



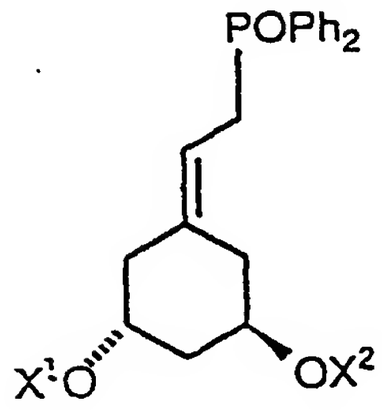

worin $X^1$ und $X^2$ die vorstehend angegebene Bedeutung besitzen, und gegebenenfalls Überführen des Alkohols in sein entsprechendes Halogen-, O-Tosyl-, O-Mesyl- oder Hydroxy-geschütztes Derivat überführt, und gegebenenfalls Entfernen der Hydroxy-Schutzgruppen $X^1$ und $X^2$, mit der Maßgabe, daß, wenn $X^3$ im obigen Ester eine geschützte Hydroxyfunktion ist, diese Funktion vor der Reduktionsreaktion durch Entfernen der Schutzgruppe eliminiert wird, und Unterwerfen des Thiono-Esterderivats des Alkohols einer reduktiven freien radikalischen Deoxygenierungsreaktion.

**11.** Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß es ferner umfaßt die Stufe des Überführens einer Verbindung der Formel X in:

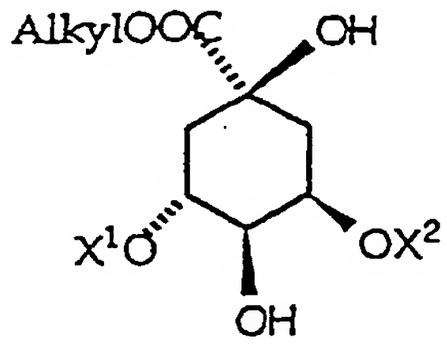



worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutzgruppe ist und $Y^1$ $-POPh_2$, $-Si(Alkyl)_3$, $-PO(OAlkyl)_2$ oder $-SO_2Ar$ ist, und Ar Phenyl oder ein Alkyl-, Nitro- oder Halogen-substituiertes Phenyl bedeutet, und Alkyl ein geradkettiges oder verzweigtes gesättigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form bedeutet.

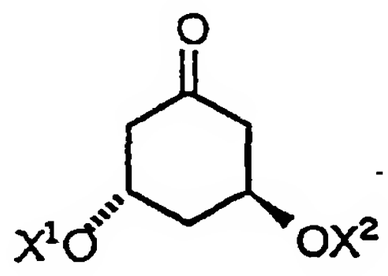
**12.** Verfahren nach Anspruch 10 zur Herstellung eines Phosphinoxids der Formel



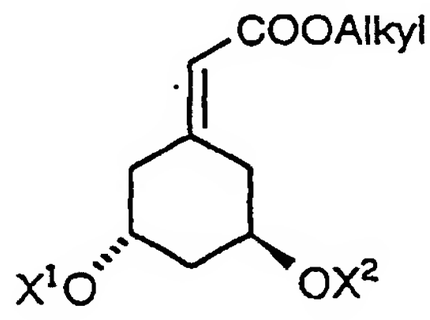
worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, Wasserstoff oder eine Hydroxy-Schutzgruppe ist, dadurch gekennzeichnet, daß man die 4-Hydroxygruppe einer Chininsäure der Formel:



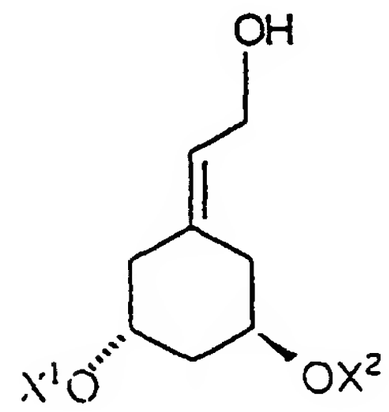
worin jeder der Reste $X^1$ und $X^2$, die gleich oder verschieden sein können, eine Hydroxy-Schutzgruppe ist, und "Alkyl" ein geradkettiges oder verzweigtes Kohlenwasserstoffradikal mit 1 bis 10 Kohlenstoffatomen in irgendeiner isomeren Form ist, eliminiert, indem man den entsprechenden Thiono-Ester mit einer Quelle für Wasserstoffradikale in Gegenwart eines radikalischen Initiators behandelt, die resultierende dehydroxylierte Verbindung in ein Keton der Formel überführt:



worin $X^1$ und $X^2$ die vorstehend angegebene Bedeutung besitzen, indem man die deoxygenierte Verbindung mit einem Hydrid-Reduktionsmittel behandelt, und danach eine oxidative Spaltung des resultierenden vicinalen Diols vornimmt, das Keton in Gegenwart von Alkyl(trimethylsilyl)acetat und einer starken Base kondensiert unter Herstellung eines Esters der Formel



worin $X^1$ und $X^2$ und "Alkyl" die oben angegebene Bedeutung besitzen, den Ester reduziert unter Erhalt eines Alkohols der Formel:

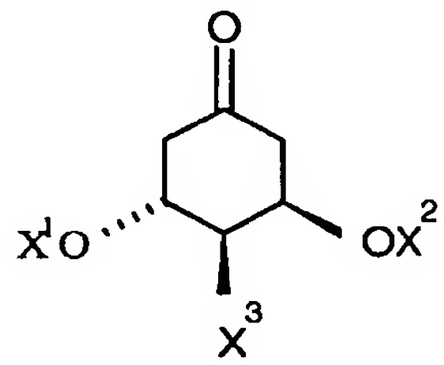


worin $X^1$ und $X^2$ die vorstehend angegebene Bedeutung besitzen, und diesen Alkohol in das entsprechende Allylchlorid oder Tosylat überführt, und danach die Chlorid- oder Tosylatgruppe mit Diphenylphosphid entfernt, und das resultierende Diphenylphosphinderivat zum Phosphinoxid oxidiert, und gegebenenfalls die Hydroxyschutzgruppen entfernt.

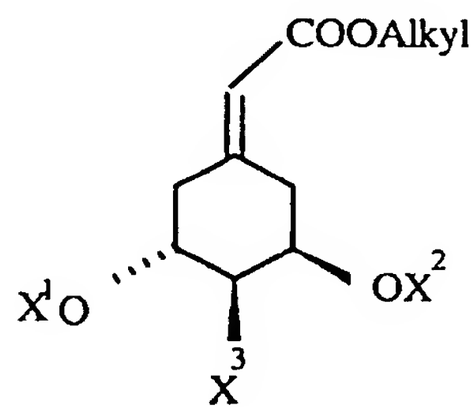
**Revendications**

1. Procédé de préparation d'un composé 19-norvitamine D, qui comprend les étapes consistant à :

   . condenser une cétone de structure :



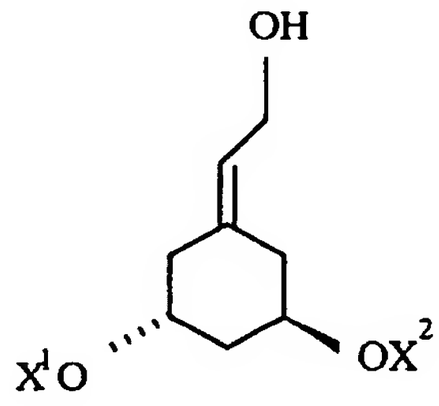
dans laquelle $X^1$ et $X^2$ représentent chacun un groupe protecteur de la fonction hydroxyle, et $X^3$ représente un atome d'hydrogène ou un groupe hydroxyle, en présence d'une base forte, pour obtenir un ester ayant la structure :




dans laquelle $X^1$, $X^2$ et $X^3$ sont tels que définis précédemment et "alkyl" représente un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque, étant

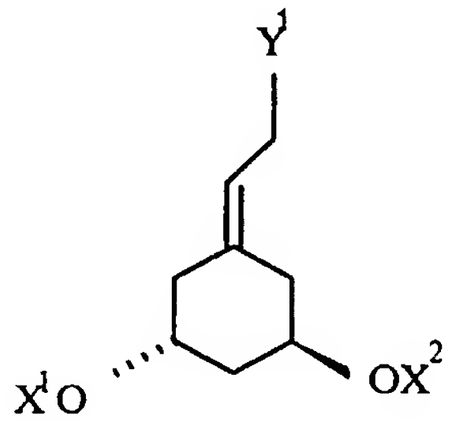
entendu que lorsque $X^3$ de la cétone précédente est un groupe hydroxyle, cette fonction hydroxyle est d'abord protégée par un groupe protecteur de la fonction hydroxyle, avant la réaction de condensation favorisée par la base,

- réduire ledit ester pour obtenir l'alcool allylique ayant la structure :



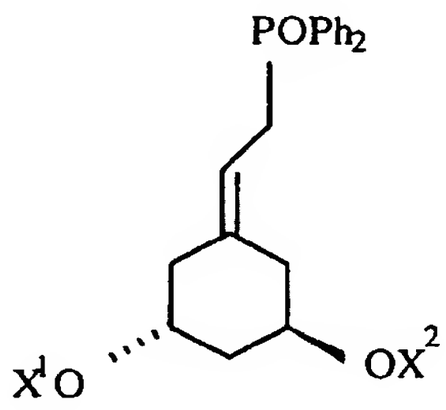
dans laquelle $X^1$ et $X^2$ sont tels que définis précédemment, étant entendu que si $X^3$ de l'ester précédent est une fonction hydroxyle protégée, on élimine cette fonction en ôtant le groupe protecteur et en transformant l'alcool libre résultant en un thiono-ester que l'on soumet à une réaction de désoxygénation par des radicaux libres réducteurs,

- transformer ledit alcool allylique en un dérivé ayant la structure :



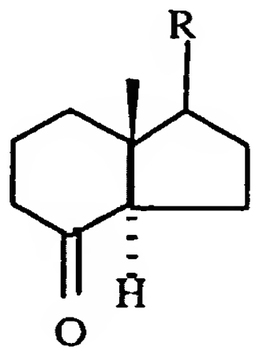
dans laquelle $Y^1$ est un atome d'halogène qui est un atome d'iode, de brome ou de chlore, ou un groupe O-tosyle ou O-mésyle, et $X^1$ et $X^2$, qui peuvent être identiques ou différents, sont des groupes protecteurs de la fonction hydroxyle,

- transformer ledit dérivé en oxyde de phosphine de structure :

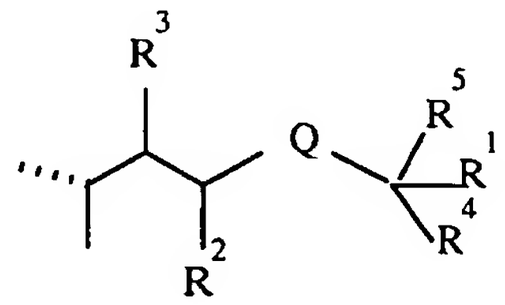


dans laquelle $X^1$ et $X^2$ sont tels que définis précédemment, par traitement dudit dérivé avec un diphénylphosphure de métal, suivi d'une oxydation par un péroxyde,

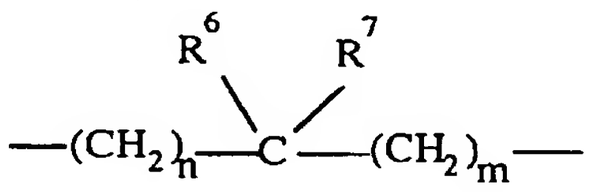
. faire réagir l'oxyde de phosphine avec une cétone de structure :



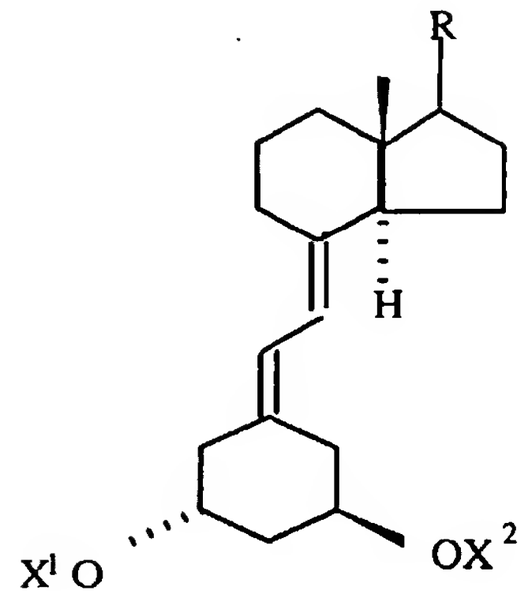
dans laquelle R représente un atome d'hydrogène, un groupe alkyle, hydroxyalkyle, deutéro-alkyle ou fluoroalkyle, la partie alkyle dudit groupe étant telle que définie précédemment pour "alkyl", ou une chaîne latérale de formule :



dans laquelle $R^1$, $R^2$, et $R^3$, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un groupe hydroxyle, un groupe hydroxyle protégé ou un groupe alkyle, ledit groupe alkyle étant un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque, la liaison entre les atomes de carbone 22 et 23 peut être une liaison simple, double ou triple, Q représente le groupe de formule :



dans laquelle $R^6$ et $R^7$, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou de fluor, un groupe alkyle, un groupe hydroxyalkyle, un groupe hydroxyle ou un groupe hydroxyle protégé, ledit groupe hydroxyalkyle étant un radical alkyle substitué par un ou plusieurs groupes hydroxyles, ou bien $R^6$ et $R^7$ pris ensemble représente un groupe oxo ou un groupe alkylidène, et n et m, qui peuvent être identiques ou différents, représentent chacun 0, 1, 2, 3, 4 ou 5, $R^4$ et $R^5$ qui peuvent être identiques ou différents, représentent chacun un groupe fluoroalkyle ou le groupe Q-H, ou bien $R^4$ et $R^5$ pris ensemble représente le groupe Q, étant entendu que lorsque $R^4$ et $R^5$ pris ensemble représente Q, au moins l'un de n et m est $\geq 1$, l'un quelconque des groupes CH aux positions 20, 22 et 23 dans la chaîne latérale pouvant être remplacé par un atome d'azote ou l'un quelconque des groupes-$CH(CH_3)$-, -$CH(R^3)$- et -$CH(R^2)$- aux positions 20, 22 et 23, respectivement, pouvant être remplacé par un atome d'oxygène ou de soufre, pour produire un composé 19-norvitamine D de structure :

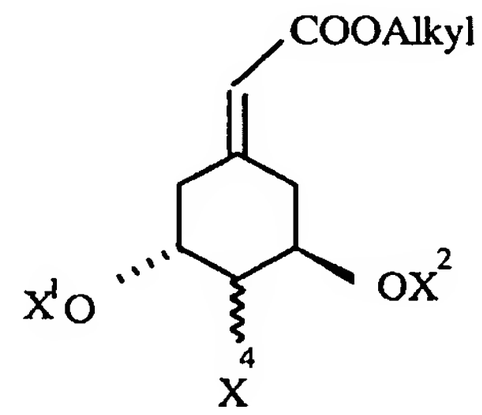



dans laquelle $X^1$, $X^2$ et R sont tels que définis précédemment, et ensuite, si on le souhaite, éliminer un ou plusieurs groupes protecteurs de la fonction hydroxyle.

2. Procédé selon la revendication 1, dans lequel on élimine les groupes protecteurs de la fonction hydroxyle, en soumettant le composé 19-norvitamine D à fonction hydroxyle protégée à une hydrolyse ou une réduction par un hydrure.

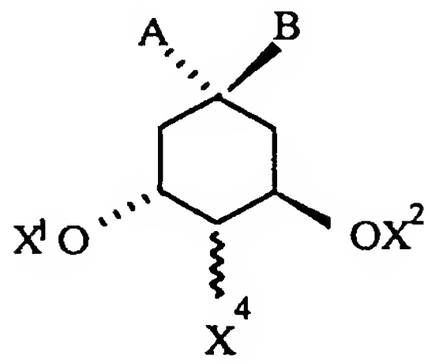
3. Procédé selon la revendication 1 ou 2, pour la production de la 19-nor-1α, 25-dihydroxyvitamine $D_3$ ou de la 19-nor-1α-hydroxyvitamine $D_3$.

4. Composé de structure :



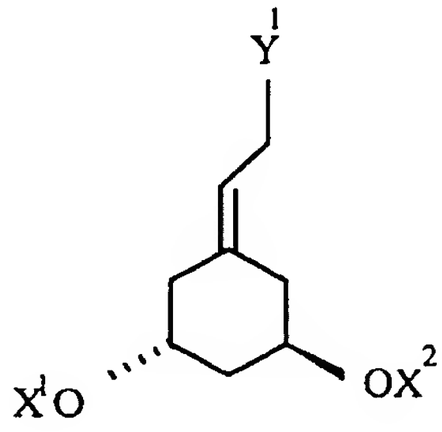

dans laquelle $X^1$ et $X^2$, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle, $X^4$ représente un atome d'hydrogène, un groupe hydroxyle ou un groupe hydroxyle protégé, et "alkyl" désigne un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque.

5. Composé de structure :



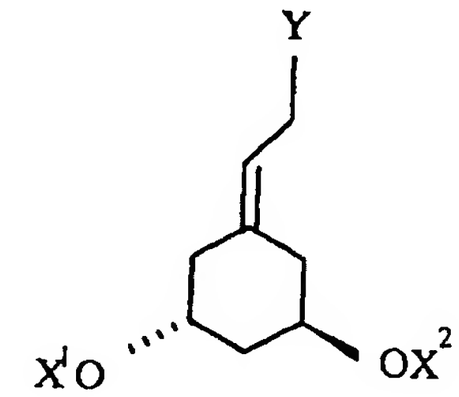
dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle, $X^4$ représente un atome d'hydrogène, A représente un groupe -COOAlkyl ou $-CH_2OH$, "alkyl" désignant un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque, et B représente un groupe hydroxyle, ou bien A et B pris ensemble représentent un groupe oxo.

6. Composé de structure :



dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle et $Y^1$ représente un groupe hydroxyle, un groupe hydroxyle protégé, un groupe O-tosyle, un groupe, O-mesyle ou un atome de brome, de chlore ou d'iode.

7. Composé de structure :

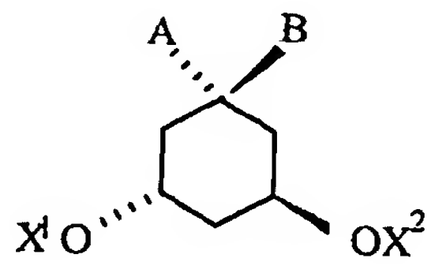


dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle et Y représente un groupe $-POPh_2$, $-PO(OAlkyl)_2$, $-SO_2Ar$ ou -Si $(Alkyl)_3$, ledit Ar représentant un groupe phényle ou un groupe phényle substitué par un groupe alkyle, un groupe nitro ou un atome d'halogène, et ledit alkyl représentant un radical hydrocarboné saturé, à chaîne droite ou ramifiée,

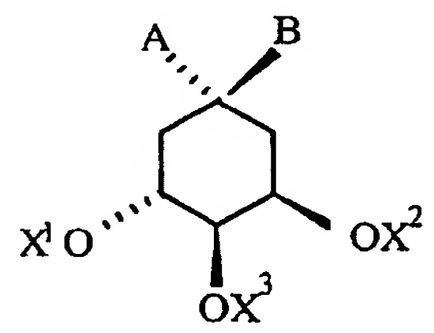
ayant 1 à 10 atomes de carbone et une forme isomère quelconque.

8. Composé selon la revendication 7, dans lequel Y représente le groupe -$POPh_2$.

9. Procédé de préparation d'un composé de formule :

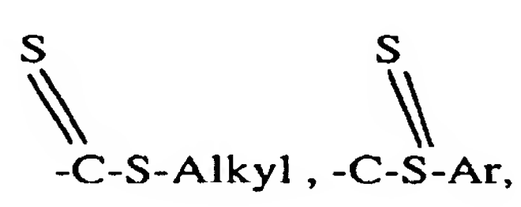


dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle, A représente un groupe -COOAlkyl ou -$CH_2OH$ et B représente un groupe hydroxyle, ou bien A et B pris ensemble représentent un groupe oxo ou =CHCOOAlkyl, "alkyl" désignant un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque, qui comprend l'élimination du groupe en position 4 d'un composé de formule :



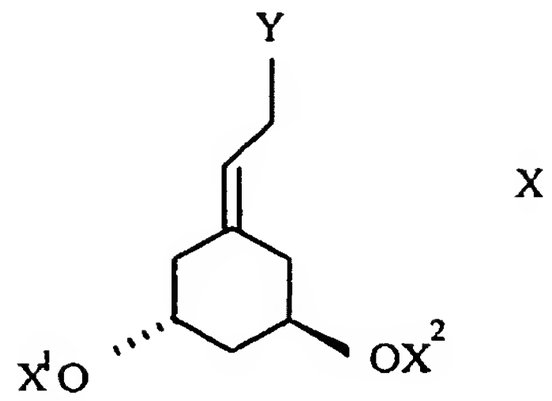
dans laquelle $X^3$ représente un groupe

ou

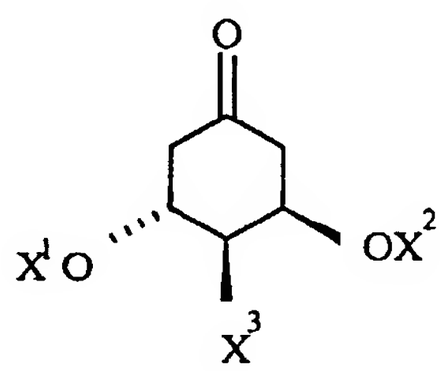


ledit Ar représentant un groupe phényle ou un groupe phényle substitué par un groupe alkyl, un groupe nitro ou un atome d'halogène, et ledit alkyl désignant un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque, élimination que l'on réalise en soumettant ledit composé à une réaction de désoxygénation par des radicaux libres réducteurs.

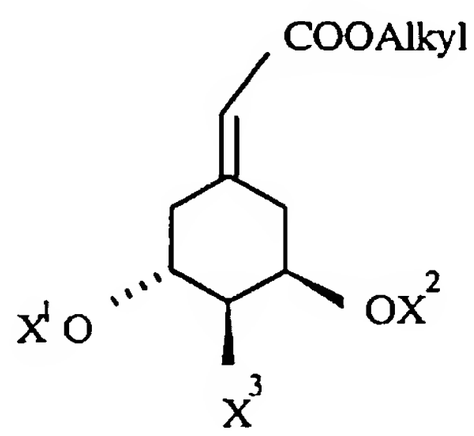
10. Procédé de préparation d'un composé de formule X :



dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle, et Y représente un groupe hydroxyle, un atome d'halogène, un groupe O-mésyle, un groupe O-tosyle ou un groupe protecteur de la fonction hydroxyle, qui comprend la condensation d'une cétone de structure :

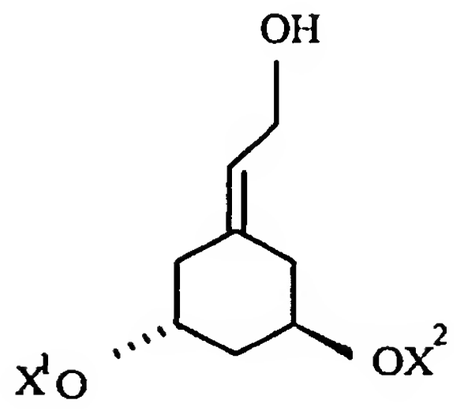


dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un groupe protecteur de la fonction hydroxyle, et $X^3$ représente un atome d'hydrogène ou un groupe hydroxyle, en présence d'une base forte, pour produire un ester de formule :



dans laquelle $X^1$ , $X^2$ et $X^3$ sont tels que définis précédemment et "alkyle" représente un radical hydrocarboné saturé, à chaîne droite ou ramifiée ayant 1 à 10 atomes de carbone et une forme isomère quelconque, étant entendu, que lorsque $X^3$ de la cétone précédente est un groupe hydroxyle, ce groupe hydroxyle est d'abord protégé par un groupe protecteur de la fonction hydroxyle, avant la réaction de condensation favorisée par la base,

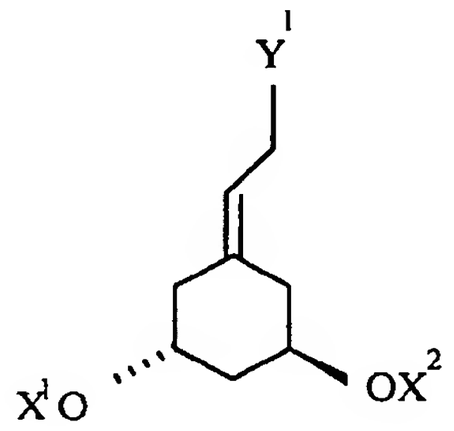
la réduction dudit ester pour produire un alcool de formule



dans laquelle $X^1$ et $X^2$ sont tels que définis précédemment, éventuellement la transformation dudit alcool en le dérivé correspondant halogéné, O-tosyle, O-mésylé ou à fonction hydroxyle protégée,

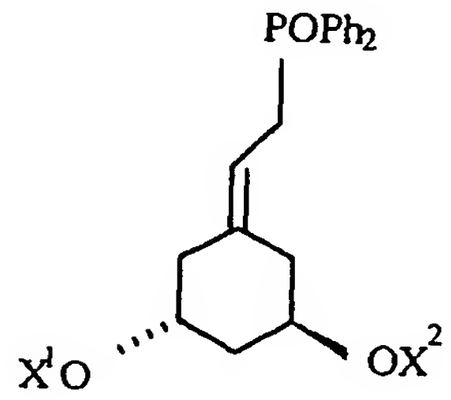
et éventuellement l'élimination des groupes $X^1$ et $X^2$ protecteurs de la fonction hydroxyle, étant entendu que si $X^3$ de l'ester précédent est un groupe hydroxyle protégé, on élimine ce groupe avant la réaction de réduction en éliminant le groupe protecteur et en soumettant le dérivé thiono-ester de l'alcool à une réaction de désoxygénation par des radicaux libres réducteurs.

**11.** Procédé selon la revendication 10, qui comprend en outre l'étape consistant à transformer un composé de formule X en un composé de formule :



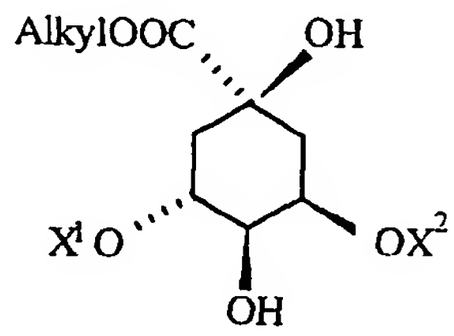
dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle et $Y^1$ représente un groupe $-POPh_2$, $Si(Alkyl)_3$ $-PO(OAlkyl)_2$ ou $-SO_2Ar$, ledit Ar représentant un groupe phényle ou un groupe phényle substitué par un groupe alkyl, un groupe nitro ou un atome halogène, et ledit alkyle désignant un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque.

**12.** Procédé selon la revendication 10, pour la préparation d'un oxyde de phosphine de formule :

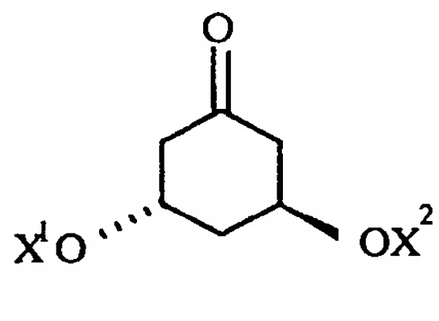


dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe protecteur de la fonction hydroxyle, qui comprend les étapes consistant à:

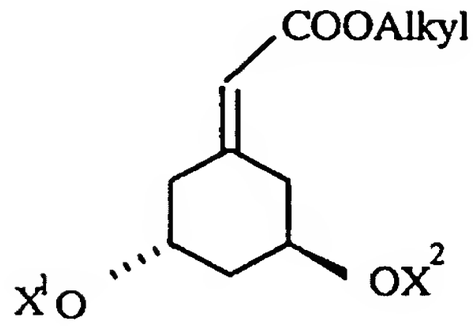
éliminer le groupe hydroxyle en position 4 d'un acide quinique de formule :



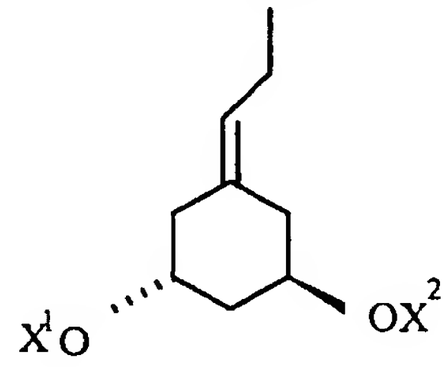
dans laquelle $X^1$ et $X^2$ qui peuvent être identiques ou différents, représentent chacun un groupe protecteur de la fonction hydroxyle et "alkyl" désigne un radical hydrocarboné saturé, à chaîne droite ou ramifiée, ayant 1 à 10 atomes de carbone et une forme isomère quelconque, en traitant le thiono-ester correspondant par une source de radicaux hydrogènes en présence d'un amorceur radicalaire,
transformer le composé déshydroxylé résultant en une cétone de formule :



dans laquelle $X^1$ et $X^2$ sont tels que définis précédemment, en traitant le composé désoxygéné par un agent réducteur de type hydrure, puis en soumettant le diol vicinal résultant à une scission par oxydation, condenser la cétone en présence d'un (triméthylsilyl) acétate d'alkyl et d'une base forte pour produire un ester de formule :




dans laquelle $X^1$, $X^2$ et "alkyl" sont tels que définis précédemment,
réduire ledit ester pour produire un alcool de formule :




dans laquelle $X^1$ et $X^2$ sont tels que définis précédemment,
transformer ledit alcool en le chlorure ou le tosylate allylique correspondant, puis remplacer le groupe chlorure ou tosylate par un groupe diphénylphosphure et oxyder la diphénylphosphine résultante en oxyde de phosphine,
et éventuellement éliminer les groupes protecteurs de la fonction hydroxyle.